A COMPARATIVE STUDY OF EQUIPOTENT DOSES OF DEXMEDETOMIDINE AND CLONIDINE AS ADDITIVE TO HYPERBARIC BUPIVACAINE IN SPINAL ANAESTHESIA

DISSERTATION SUBMITTED FOR THE DEGREE OF

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BRANCH – X (ANAESTHESIOLOGY)

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THE TAMILNADU

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CHENNAI, TAMILNADU

BONAFIDE CERTIFICATE

This is to certify that this dissertation entitled **"A COMPARATIVE STUDY OF EQUIPOTENT DOSES OF DEXMEDETOMIDINE AND CLONIDINE AS ADDITIVE TO HYPERBARIC BUPIVACAINE IN SPINAL ANAESTHESIA."** is a bonafide record work done by **Dr. C.GOWRI SANKAR** under my direct supervision and guidance, submitted to the Tamil Nadu Dr. M.G.R. Medical University in partial fulfilment of University regulation for MD, Branch X –Anaesthesiology.

PROF. Dr.T.THIRUNAVUKKARASU, M.D, D.A,

Director, i/c.
Institute of Anaesthesiology,
Govt. Madurai Medical College & Hospital
Madurai.

DECLARATION

I **Dr.C. GOWRI SANKAR** solemnly declare that this dissertation titled **"A COMPARATIVE STUDY OF EQUIPOTENT DOSES OF DEXMEDETOMIDINE AND CLONIDINE AS ADDITIVE TO HYPERBARIC BUPIVACAINE IN SPINAL ANAESTHESIA"** has been done by me. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, diploma to any other University or board either in India or abroad.

This is submitted to The Tamilnadu Dr. M. G. R. Medical University, Chennai, in partial fulfilment of the rules and regulation for the award of Doctor of Medicine degree Branch –X (Anaesthesiology) to be held in April 2012.

Place: Madurai Dr. C.GOWRI SANKAR

Date:

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A COMPARATIVE STUDY OF EQUIPOTENT DOSES OF DEXMEDETOMIDINE AND CLONIDINE AS ADDITIVE TO HYPERBARIC BUPIVACAINE IN SPINAL ANAESTHESIA

ABSTRACT

Background: The purpose of this study was to compare the onset and duration of sensory and motor block, as well as the hemodynamic changes and level of sedation, following intrathecalbupivacaine supplemented with either dexmedetomidine or clonidine**.**

Methods: In a prospective, double-blind study, 94 patients undergoing infra- umblical surgeries under spinal anesthesia were randomly allocated to one of three groups. Group B received 12.5 mg of hyperbaric bupivacaine, group D received 12.5 mg of bupivacaine supplemented with 5 µg of dexmedetomidine and group C received 12.5 mg of bupivacaine supplemented with 50 µg of clonidine. The onset times to reach peak sensory and motor levels, and the sensory and motor regression times, were recorded. Hemodynamic changes and the level of sedation were also recorded.

Results: Patients in groups D and C had a significantly shorter onset time of motor block and significantly longer sensory and motor regression times than patients in group B. The mean time of sensory regression to the S1 segment was 337 min in group D, 265 min in group C and 179 min in group B (B vs. D and B vs. C, $P < 0.001$). The regression of motor block to Bromage 0 was 262.41 min in group D, 205.9 min in group C and 148.55 min in group B (B vs. D and B vs. C, $P < 0.0001$). The onset and regression times were significantly different between groups D and C. Both Clonidine and dexmedetomidine lowered the pulse rate, systolic BP, diastolic BP. But clonidine's lowering of SBP was significant and sustained for a prolonged period. Similarly clonidine produced a much deeper and prolonged plane of sedation in comparison to dexmedetomidine.

Conclusions: In comparision to clonidine (50 µg), Dexmedetomidine (5 µg) when added to intrathecal bupivacaine, produces a prolonged duration of the motor and sensory block with better hemodynamic stability.

Key words: α2 adrenergic agonist, Clonidine, Dexmedetomidine, hyperbaric bupivacaine, Spinal anaesthesia.

AIM OF THE STUDY

To compare the effect of addition of equipotent doses of Clonidine (50 μg) and Dexmedetomedine (5 μg) in 0.5 ml normal saline, respectively added to 2.5 ml of 0.5% Hyperbaric Bupivacaine (making it a total of 3 ml) in spinal anaesthesia for sub umbilical surgeries

To evaluate:

- Time to onset of sensory and motor block
- Duration of sensory and motor block
- Duration of effective post operative analgesia
- Side effects

INTRODUCTION

Spinal anaesthesia is commonly used for abdominal, perineal, gynaecological and lower limb operations. It offers excellent anaesthesia and fewer side effects than general anaesthesia. It is easy to perform and provides faster onset and effective sensory and motor block. Bupivacaine produces long lasting spinal anaesthesia without transient neurological symptoms. Recently there has been an interest in using additives to intra thecal local anasesthetics to decrease the dose of local anaesthetics and also to provide effective post operative analgesia.

Dexmedetomidine an α2-adrenergic agonist that has been used for pre-medication and as an adjunct to general anesthesia as well as a sole anesthetic agent and also as a sedation agent in the intensive care unit[31,26]. Dexmedetomidine has been used intrathecally in animals and was found to be a very potent antinociceptive agent[32-34]. It has been used in the epidural space in humans without any reports of neurological deficits[35]. Dexmedetomidine used intravenously, significantly prolonged the sensory and motor block of spinal Prilocaine[36]. Dexmedetomidine (3 μg) with Bupivacaine, as spinal anesthetic, in humans, produced shorter onset and prolonged the duration of motor and sensory block with hemodynamic stability and lack of sedation[37]. Clonidine is an α2-adrenergic agonist that is often administered intrathecally in humans. It has been given in doses upto

450 µg in dosing studies, but was found that the duration of both sensory and motor block plateaued at 150 µg of Clonidine[32-34,39]. Animal studies[32,34], had shown that a 1:10 dose ratio between intrathecal Dexmedetomidine and Clonidine, produced a similar effect. The potency of an epidurally administered α2-adrenergic agonist was well correlated with their binding affinity to the spinal α2-adrenergic receptor. Therefore, we used larger equipotent doses of Dexmedetomidine (5 µg) and Clonidine (50 µg) in the spinal anesthesia combined with Bubivacaine than previous study to investigate the effect of adding this doses on the onset and regression of sensory and motor block together with hemodynamic and sedation changes versus intrathecal Bupivacaine alone.

SPINAL ANAESTHESIA AND ADJUVANTS

Spinal (subarachnoid/intrathecal) anaesthesia is a form of central neuraxial block in which a temporary interruption of nerve transmission is achieved following injection of local anaesthetic/ adjuvant solutions into subarachnoid space.

Subarachnoid block is one of the most commonly performed methods of regional anaesthesia.

Anatomy

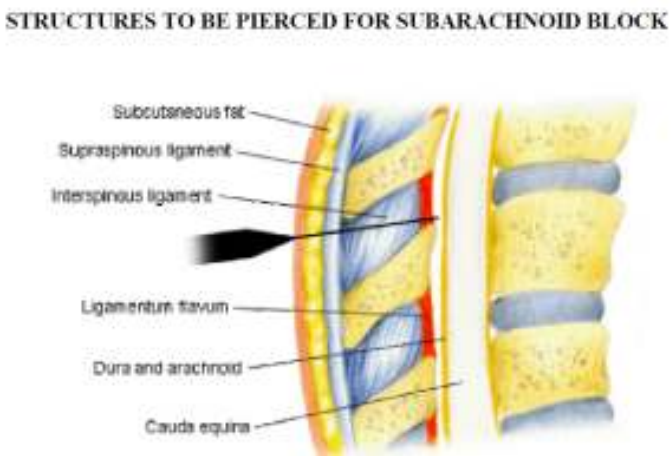
The vertebral canal extends from foramen magnum to the sacral hiatus. Its boundaries are the dorsal spine, pedicles and laminae of successive vertebrae (7 cervical, 12 thoracic, 5 lumbar and 5 sacral). The vertebrae are held together by overlapping ligaments namely, anterior and posterior longitudinal ligaments, ligamentum flavum, interspinous ligament, supraspinous ligament and the intervertebral discs.

The spinal cord is a direct continuation of medulla oblongata, begins at the upper border of atlas and terminates distally in the conusmedullaris. The distal termination, because of the differential growth rates between the bony vertebral canal and spinal cord varies from L3 in the infant to lower border of L1 in the adult.

Surrounding the spinal cord in the bony vertebral column are 3 membranes (from within to periphery): the pia mater, arachnoid mater and the dura mater. The pia mater is a highly vascular membrane that closely invests the spinal cord. The arachnoid mater is a delicate non vascular membrane closely attached to outermost dura mater.

STRUCTURES TO BE PIERCED FOR SUBARACHNOID BLOCK

Between the 2 innermost membranes is the subarachnoid space. In this space, cerebrospinal fluid (CSF), spinal nerves, blood vessels that supply the spinal cord and dentate ligaments are present. Although the spinal cord ends at lower border of L1 in adults, the subarachnoid space continues upto S2. The outermost membrane in the spinal cord is the longitudinally organised fibroelastic membrane, the dura mater. This layer is the direct extension of cranial dura mater and extends as spinal dura mater from foramen magnum to S2, where filum terminale blends with periosteum of subdural space which contains small amounts of serous fluid to allow dura and arachnoid to move over each other.



Surrounding the dura mater is the epidural space which extends from foramen magnum to sacral hiatus. Posterior to the epidural space is ligamentum flavum. Immediately posterior to the ligamentum flavum is interspinous ligament. Extending from external occipital protruberance to the coccyx, posterior to this structure is the supraspinous ligament.

Lumbar puncture is routinely performed below L2 vertebrae down to the L5-S1 interspace to avoid damage to the spinal cord which ends at lower border of L1 vertebra in adults.

PHYSIOLOGY OF SUBARACHNOID BLOCK

Cerebrospinal Fluid

The cerebrospinal fluid is an ultrafiltrate of blood plasma which is in hydrostatic and osmotic equilibrium. It is clear, colourless fluid found in spinal and cranial subarachnoid space and in ventricles of brain. The average volume in adults ranges from 120 to 150 ml of which 35 ml in the ventricles, 25 ml is in the cerebral subarachnoid space and 75 ml is in the spinal subarachnoid space. It is secreted by choroid plexus at a rate of 0.3 - 0.4 ml/minute.

Physical Characteristics of Cerebrospinal Fluid

- pH 7.4
- Specific gravity 1.007
- Density 1.0003
- Baricity 1.000
- Pressure 8-12 mmHg / 70- 80 cm H_20
- Cells 3- 5 /cu.mm
- Proteins 20 mg/dl
- Glucose 45 -80 mg/dl

The cerebrospinal fluid plays an important role in spinal anaesthesia as a media for dispersion of the local anaesthetic drug to the spinal nerve. An important factor determining the spread of drugs in subarachnoid space is specific gravity of the injected solution compared with that of CSF.

MECHANISM OF SPINAL ANAESTHESIA

Injection of local anaesthetics into the spinal CSF allows access to sites of action both within the spinal cord and the peripheral nerve roots. The nerve roots leaving the spinal canal are not covered by epineurium and are readily exposed to the local anaesthetic within CSF. Therefore afferent impulses leaving via ventral nerve roots are blocked during spinal anaesthesia. Spinal local anaesthetics block sodium channels and electrical conduction in spinal nerve roots. Local anaesthetics can exert sodium

channel block within the dorsal and ventral horns inhibiting the generation and propagation of electrical activity.

The order in which nerve fibres are blocked in spinal anaesthesia is preganglionic sympathetic B fibres followed by temperature fibres (cold before warmth), fibres carrying pin prick sensation, touch, deep pressure and finally proprioception. Recovery is in the reverse order. The major factors determining the level of blockade after subarachnoid block are the baricity of the local anaesthetic solution, the position of the patient before and after injection and dose of the anaesthetic injected.

Fate of Local Anaesthetics in Subarachnoid Space

Following injection of local anesthetic solution into subarachnoid space, its concentration falls rapidly. The initial steep fall is due to mixing with CSF and subsequent absorption into nerve roots and spinal cord. Depending on the type of drug used, it is metabolized in plasma by pseudocholinesterase or in the liver. The addition of a vasopressor to the local anesthetic will retard the absorption of the drug and thus increase the duration of anaesthesia.

Indications for subarachnoid block

Spinal anaesthesia can be administered whenever a surgical procedure can be done with a sensory level of anaesthesia that does not produce adverse patient outcome which includes,

- Lower abdominal surgeries
- Lower limb surgeries
- Urological procedures
- Obstetric & gynaecological procedures
- Perineal and rectal surgeries

Contra indications for subarachnoid block

An absolute contraindication for subarachnoid block is patient refusal.

Other contraindications are:

- Local sepsis
- Uncorrected coagulopathy
- Uncontrolled blood loss / shock
- Fixed cardiac output states
- Documented allergy to local anaesthetics
- Raised intracranial pressure
- Neurological disease
- Major spine deformities /previous surgery on the spine
- Severe cardiac disease.

Spinal Anaesthesia Technique

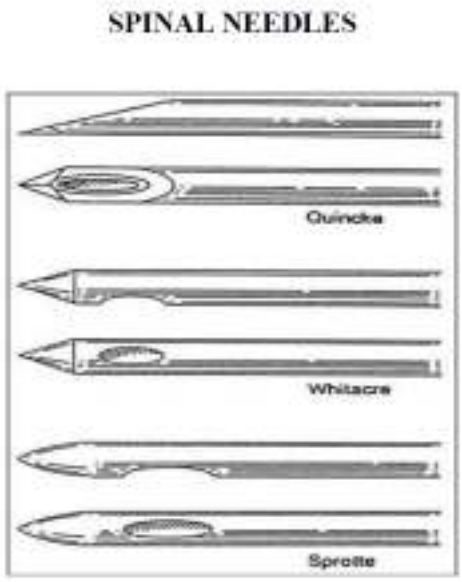
The first step in successful application of spinal anaesthesia is proper patient selection. This is accomplished by pre-anaesthetic evaluation of the

patient through history, physical examination, laboratory data and communication with patient and surgical staff about details of the procedure. Reliable intravenous access through a large bore intravenous canula (18G /16G) is mandatory. Preloading limits the hypotension that may result from sympathetic block. The recommended standards for airway management and emergency drugs are kept in readiness.

PROCEDURE

Preparation

Preparation of equipment and drugs is essential for performing a subarachnoid block. The choice of drug is based on duration of block desired, the surgical procedure and patient variables. Spinal needles of various diameters with various types of points are available. Spinal needles fall into two main categories: those that cut the dura and those that are designed to separate the dural fibres former includes the Quincke-Babcock needle and the latter include the Greene, Whitacre and Sprotte needles. In order to keep the incidence of post dural puncture headache to a minimum, small bore needles with a rounded non-cutting bevel are preferred.



POSITION

The choice of position of the patient for performing the subarachnoid block depends on a number of factors - the proposed surgery being the most important.

LATERAL DECUBITUS POSITION

Lateral Decubitus Position

In the lateral decubitus position, the patient is placed with back parallel to the edge of the operating table nearest the anaesthesiologist with thigh flexed upon the abdomen and neck flexed.

Sitting Position

The sitting position is chosen when low lumbar and sacral levels of anaesthesia are adequate for the surgical procedure or when obesity or scoliosis makes identification of midline anatomy difficult in lateral decubitus position or when orthopaedic problems of hip and knee exist.

Projection and Puncture

The spinal puncture can be performed either by a midline or a paramedian approach, usually at the L2-L3, L3-L4, L4-L5 interspaces. The procedure is carried out under strict aseptic conditions.

The patients back is prepared with an antiseptic solution and sterile drapes are applied. A line from the highest point of iliac crest passes through either spinous process of L4 or the L4-L5 interspace. The midline approach with the patient in sitting position /right lateral decubitus position is used in our study. Depending on the interspace and approach selected, subcutaneous skin wheal is raised over the intended puncture site with local anaesthetic solution. The needle is inserted in the middle of the interspace with bevel parallel to the longitudinal dural fibres. After traversing the skin and subcutaneous tissue, the needle is advanced in a slightly cephalad direction with the long axis of the vertebral column. The stylet is removed and appearance of cerebrospinal fluid at the hub of the needle confirms correct position of the needle tip. Stylet is reinserted to prevent excess leakage of CSF. The hub of the needle is firmly held between the thumb and index finger of the anaesthesiologist's non dominant hand and back of hand held against patients back to steady the needle, while syringe containing anaesthetic solution is firmly attached to the needle.

After confirming free flow of spinal fluid by aspiration, the anaesthetic solution is injected. The patient is placed in supine position. Cardiovascular and respiratory functions are monitored. Analgesia is checked by loss of sensation to pin prick. Motor block assessed by modified Bromage score.

In the recent past various additives have been added to local anaesthetic solution - vasopressors, opioids, alpha 2 adrenergic agonists and acetyl choline esterase inhibitors. These produce prolongation of analgesia after subarachnoid block and reduce the dose requirement of local anaesthetics.

COMPLICATIONS OF SUB ARACHNOID BLOCK

Immediate

1. Hypotension
2. Bradycardia
3. Toxicity due to intravascular injection
4. Allergy to local anaesthetic
5. Hypoventilation (brainstem hypoxia)

Late

1. Post dural puncture headache
2. Retention of urine

3. Backache

4. Meningitis

5. Transient lesions of cauda equina

6. Sixth nerve palsy

7. Anterior spinal artery syndrome

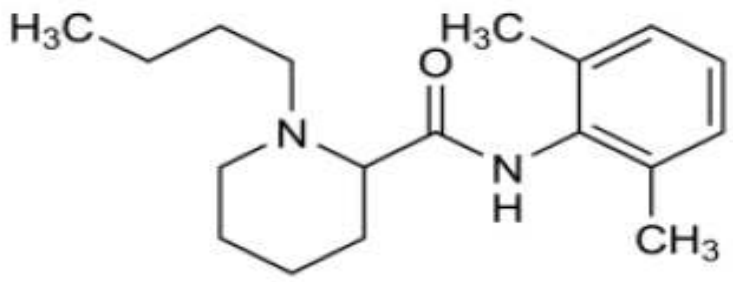
PHARMACOLOGY OF BUPIVACAINE

Bupivacaine is an amide local anaesthetic synthesised by A.F.Ekenstam in 1957 and brought into clinical use in 1963.

It is produced for clinical use in a racemic mixture containing equal proportions of the 'S' and 'R' enantiomers. It is supplied for clinical use as hydrochloride salt.

Chemical structure

BUPIVACANE HYDROCHLORIDE



Description: +1-butyl-N-(2,6-dimethylphenyl)-2-piperidine Decarboxamide Hydrochloride monohydrate.

Physio-chemical profile:

Molecular weight (base)	-	288
pKa	-	8.1

Solubility In:

Alcohol	-	1 in 8

Water	-	1 in 25
Octanol/water partition coefficient	-	high
Lipid solubility	-	28
Plasma protein binding	-	95%

Mechanism of action

Bupivacaine exerts its effect by inhibition of sodium channels. It acts to block conduction in nerves by decreasing or preventing the large transient increases in permeability of cell membrane to sodium ions that follows depolarisation of the membrane. Bupivacaine also reduces the permeability of the resting nerve membrane to potassium as well as sodium ions.

Pharmacodynamics

Bupivacaine by virtue of its pharmacological effects has a stabilizing action on all excitable membranes. The clinical profile of nerve blockade produced by bupivacaine differs from that of lignocaine.

It is 4 times more potent than lignocaine, but the onset of action is slower. The duration of action is considerably longer. The sensory block produced by bupivacaine tends to be more marked than the motor block.

Pharmacokinetics

Bupivacaine is rapidly absorbed from the site of injection. The rate of rise in plasma bupivacaine concentration and the peak plasma

concentrations depend on the route of administration. There is also some inter individual variation and peak systemic concentrations may occur 5 and 30 mins after administration. The addition of vasoconstrictor delays absorption and results in lower plasma concentrations of bupivacaine.

Pharmacokinetic profile [6]

Volume of distribution at steady state (Vdss)	72 litres
Clearance	0.47 l/min
t l/2 α	2.7 min
t l/2β	28 min
t l/2γ	3.5 hrs

Metabolism

Possible pathways for metabolism of bupivacaine include aromatic hydroxylation, N dealkylation, amide hydrolysis and conjugation. Only the N-dealkylated metabolite, N-desmethyl bupivacaine has been measured in blood and urine after epidural and spinal administration. The degradation of bupivacaine takes place in the liver. Renal disease is unlikely to alter the kinetics of bupivacaine to any great extent. Less than 10% of the drug is excerted unchanged in urine[6].

Clinical applications

- Infiltration anaesthesia

- Peripheral nerve blocks

- Central neuraxial blocks (intrathecal, epidural, caudal)

Contraindications

- Paracervical block (in obstetrics)

- Known hypersensitivity to amide local anaesthetics

- Intra venous regional anaesthesia (IVRA)

Preparations available

- 0.25%, 0.5% solutions in l0 ml and 20 m1 vials
- 5 mg/ml (0.5%) bupivacaine and 80 mg dextrose in 4 m1 ampoules for intrathecal injection (Baricity 1.0207)

Recommended safe dose

Concentration used	Max permitted dose
0.125% - 0.5%	3 mg/kg body weight
0.75% (not to be used in obstetric epidurals)	Max over 4 hrs - 150 mg Max during 24 hrs - 4000 mg
0.5% plain/hyperbaric (intrathecal use)	20 mg

Adverse reactions

Adverse reactions are associated with excess plasma levels of the drug which may be due to overdosage, unintentional intravascular injection or slow metabolic degradation.

CNS Reactions

Excitation characterized by restlessness, anxiety, dizziness, tinnitus, blurred vision or tremors possibly proceeding to convulsions, followed by drowsiness, unconsciousness and cardiac arrest.

CVS

Part of the blockade that occurs from high plasma concentrations of bupivacaine occurs because of blockade of cardiac sodium channels. Accidental intravenous injection of bupivacaine causes cardiac dysarrythmias, atrioventricular block, refractory ventricular tachycardia and ventricular fibrillation. Pregnancy increases the sensitivity of cardiotoxic effects of bupivacaine.

Bupivacaine binds and inhibits cardiac voltage gated calcium and potassium channels at concentrations greater than those at which binding to sodium channel is maximal.

Unlike other local anaesthetics, bupivacaine dissociates from blocked sodium channels at a much slower rate, resulting in prolongation of

maximal rate of depolarization (Vmax) and creating the potential for re-entrant type of ventricular arrhythmias.

Allergic reactions

Manifests as urticaria, pruritis, angioneurotic edema etc. Cross sensitivity among members of amide local anaesthetics has been reported.

PHARMACOLOGY OF CLONIDINE HYDROCHLORIDE

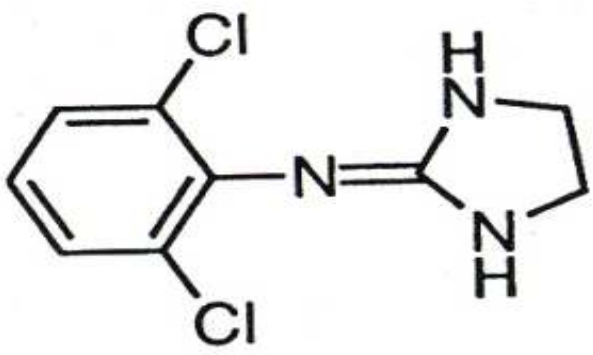
Clonidine a imidazoline derivative is a selective partial agonist for alpha 2 adrenergic receptors. It is known to increase sensory and motor block of local anaesthetics.

Its action is mediated spinally through activation of post synaptic alpha 2 receptors in the substantia gelatinosa of spinal cord.

Physical chemistry

$C_9H_9N_3\ Cl_2HCl$

STRUCTURE OF CLONIDINE



Clonidine

2,6 DichloroN-2 imidazolidinyiedlenebenzenarnine : hydrochloride

1.	Molecular weight (free base)	266.6 (230.1)
2.	pKa	8.05
3.	Solubility in alcohol	1 in 25
4.	Solubility in water	1 in 13

5. Octanol/water partition co-efficient 3.02

Clonidine hydrochloride is a white crystalline, odourless powder with a bitter taste.

Pharmacology

Clonidine is a partial agonist at alpha 2 adrenoceptors both within the central nervous system and in the periphery. It is more specific for alpha 2 than for alpha 1 with a ratio of affinities at these sites at approximately 300:1. Within the CNS alpha 2 adrenoceptors are located both presynaptically on terminals of neurons which release a variety of transmitters (nor epinephrine, epinephrine, serotonin and acetylcholine) and post synaptically on noradrenergic neurons.

Mechanism of Clonidine as an adjuvant in central neuraxial blockade

Intrathecal clonidine increases the duration of both sensory and motor block. The mechanism of clonidine induced potentiation of sensory block in spinal anaesthesia is mediated by presynaptic (inhibition of transmitter release) and post synaptic (enhancing hyperpolarisation)

The reason for potentiation of motor block seems to be hyperpolarisation of ventral horn neurons of spinal cord. This is dose related.

Clonidine blocks conduction of C and A delta fibres and increases potassium conductance in neurons and also intensifies conduction block of local anaesthetics. Clonidine may cause local vasoconstriction[12].

EFFECTS ON ORGAN SYSTEMS

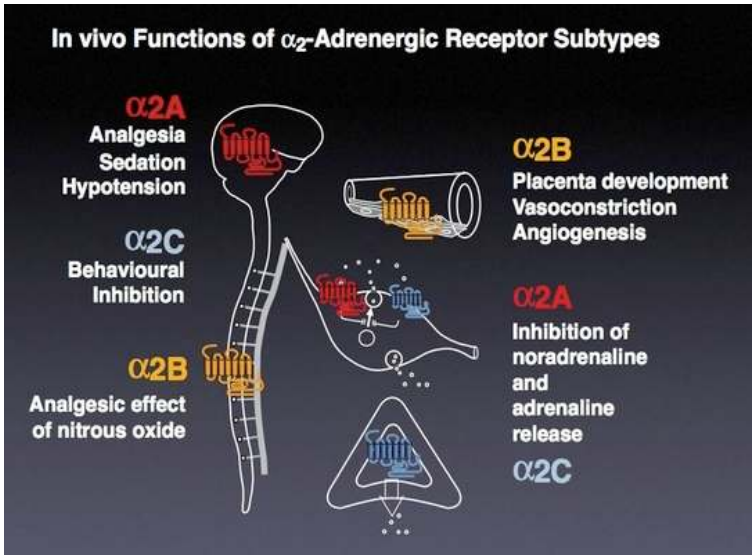
Cardiovascular System

Oral or intra venous administration of Clonidine causes a dose dependent fall in blood pressure and heart rate in both supine and erect position, with the orthostatic response being most prominent

Clonidine affects blood pressure in a complex fashion. In nucleus tractus solitarius and locus ceruleus of brain stem activation of post synaptic alpha 2 adrenoreceptors reduces sympathetic drive. In addition it activates noradrenergic binding sites in lateral reticular nucleus thereby producing hypotension and antiarrythmogenic action. The magnitude of hypotensive effect is greater in hypertensive than in normotensive subjects[12].

The brainstem and peripheral effects of alpha 2 adrenoreceptor stimulation are counter balanced by direct peripheral vasoconstriction from circulating concentrations of Clonidine. As a result the dose response for Clonidine by neuraxial or systemic administration is U shaped, with peripheral vasoconstriction from circulating drug concentrations at high doses opposing central sympatholysis.

Neuraxial administration of Clonidine directly inhibits sympathetic preganglionic neurons in spinal cord. Degree of hypotension is related to spinal level of injection.



The pressor effect of high dose of Clonidine is due to peripheral vasoconstriction mediated by stimulation of post synaptic alpha 1 and/or alpha 2 adrenoreceptors on vascular smooth muscle[21].

Respiratory System

The respiratory depressant effect of Clonidine is not remarkable unless massive doses are given. The effect of clonidine is less potent than that of opiate narcotics[23].

Central Nervous System[20]

Sedation is one of the most consistent effects mediated by central alpha 2 receptors. The locus ceruleus was shown to be the principal region responsible for sedative effect. Another characteristic effect of alpha 2 agonists is anxiolysis which is comparable to the response produced by benzodiazepine compounds.

Clonidine has a potent analgesic action that cannot be reversed by naloxone, an opioid antagonist, indicating that clonidine and opioid mediate analgesia through independent receptor mechanism. Clonidine may potentiate the effects of bupivacaine by reducing spinal cord blood flow and prolonging the effective availability of bupivacaine.

There is a 50% decrease in MAC of inhalational anesthetics and decreased anaesthetic requirements of opioids. At doses of 75 μg, it prevents shivering. Clonidine is also effective in suppressing signs and symptoms of withdrawal from opioids, benzodiazepines and ethanol.

Endocrine

Endocrine and metabolic effects mediated by alpha 2 adrenoreceptor stimulation are

1. Increased TSH and GH secretion

2. Decreased ACTH and ADH secretion

3. Inhibition of glucose stimulated insulin release, but this does not result in severe hyperglycemia in a clinical setting.

GIT

Stimulation by Clonidine of peripheral presynaptic alpha2 adrenoreceptors on post ganglionic noradrenergic or cholinergic neurons

contributes to reduced salivary flow, intestinal motor activity and gastric acid secretion.

Pharmacokinetics

- Oral absorption 100%
- Pre systemic metabolism 0-25%
- Elimination half life 20-25 h
- Volume of distribution 2 l/kg
- Plasma protein binding 20-40%

Clonidine is approximately 60% excreted unchanged in urine. The remaining 40% elimination is by oxidative metabolism predominantly in the liver. There is no evidence that any metabolites possess significant biological activity. Clearance of Clonidine is linearly related to dose over 75-300 μg. Total plasma clearance is 3 ml/kg/min, while renal clearance accounts for 1.8 ml/kg. Clearance may be reduced in the presence of abnormal renal functions. Although Clonidine may cross the placenta it does not appear to reach concentrations sufficient to affect the fetus.

Metabolism

Clonidine is approximately cleared by metabolism predominantly in the liver to five inactive metabolites the predominant pathways are: hydroxylation of the phenyl ring and opening up of the imidazoline ring following an initial reductive step with subsequent oxidative cleavage. The

hydroxylated metabolites are subjected to secondary conjugation with sulphate or glucoronide prior to urinary excretion.

DOSAGE OF CLONIDINE IN VARIOUS ROUTES

S. No.	Route	Bolus	Cont. infusion
1	Oral	4- 5 µg/kg	
2	IM	2 µg/kg	
3	IV	4- 5 µg/kg	
4	Epidural	75- 450 µg	12.5-70 µg/h
5	Intrathecal	30-225µg	8 -400 µg/day

USAGE

1. Antihypertensive agent
2. Anaesthesia - prolongation of action of local anaesthetic after neuraxial administration, pre- medication and post anaesthetic shivering
3. Opiate withdrawal syndrome
4. Glaucoma (Apraclonidine and Brimonidine)
5. Migraine prophylaxis
6. Provocative tests of growth hormone secretion, in the investigation of short stature
7. Diagnosis of phaeochromocytoma
8. Psychiatric disorders
9. Menopausal symptoms
10. Chronic diarrhea

Contraindications

Disorders of cardiac impulse generation and conduction like Sino atrial disease (Sick Sinus Syndrome), Atrioventricular node disease and patients with cardiac pacemakers.

Adverse Reactions

Common symptomatic effects are sedation (35-100%), dry mouth (25-90%), bradycardia, constipation and contact dermatitis (transdermal clonidine). Less common effects include postural hypotension, dizziness, fluid retention (weight gain, oedema), sleep disturbances (insomnia, sleep reversal, nightmares, hallucinations, reduction of REM sleep), impotence, parotid swelling and depression. Uncommon effects are rash, pruritis, angioedema, hepatitis, gynecomastia, raynauds phenomenon, thinning of hair, urinary retention and agitation.

Withdrawal syndrome which is characterised by a rapid rise in blood pressure, with marked blood pressure lability, symptoms such as headache, flushing, sweating, insomnia, agitations, emotional lability, tremor, nausea and vomiting presents 18-72 h after the last dose of clonidine. The syndrome can be prevented by gradual withdrawal of clonidine over days to weeks and, if present controlled by reintroducing clonidine treatment or by inhibiting peripheral sympathetic nervous activity, with alpha and beta adrenoreceptor antagonists.

Disturbance of cardiac impulse generation and conduction in the presence of pre existing SA and AV node disease can lead to symptomatic bradycardia and impairment of atrio ventricular (AV) nodal conduction (Wenkebach phenomenon, AV dissociation) which have been occasionally described.

PREPARATIONS

Oral forms

1. Catapres tablets (Boehringer Ingeiheirn, UK) containing clonidine hydrochloride l00 µg, 200 µg or 300 µg.
2. Dixarit tablets (Boehringer Ingeiheim, UK) containing clonidine hydrochloride 25 µg.

Transdermal form

Catapres TTS delivering clonidine l00 µg, 200 µg or 300 µg daily for 1 week.

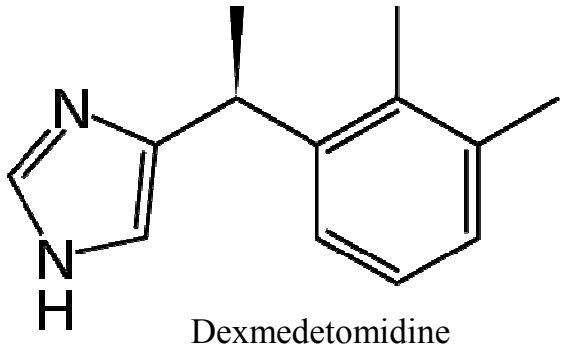
Parenteral form

1. Catapres injection (Boehringer Ingeiheim, UK) containing clonidine hydrochloride 150 µg/ml ampoules
2. CLONEON (Neon labs ltd, thane) containing clonidine hydrochloride 150 µg/ml ampoule.

PHARMACOLOGY OF DEXMEDETOMIDINE

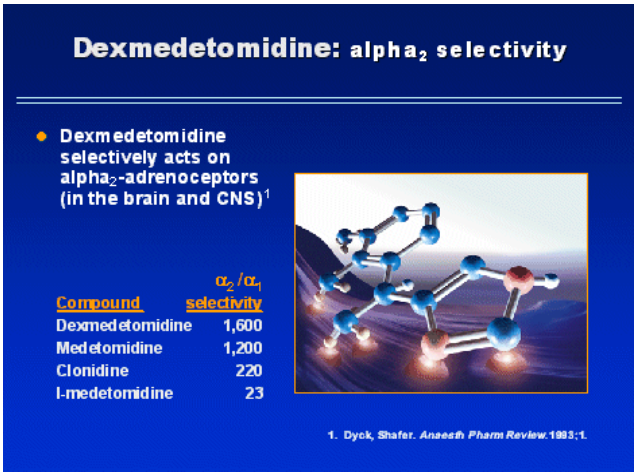
Dexmedetomidine hydrochloride is a 4-((s)-alpha,2,3-trimethyl benzyl) imidazole monohydrochloride or 4-[(1r)-1-(2,3-dimethylphenyl) ethyl]-3h-imidazole hydrochloride.

Molecular weight-236.74



Dexmedetomidine is a new alpha 2-agonist used as a short-term (less than 24 h) sedative analgesic in the intensive care unit. When compared to Clonidine is a much more selective alpha 2-adrenoceptor agonist, the alpha2/alpha1 selectivity of dexmedetomidine is 1620 and hence is 8 times more powerful alpha2-adrenoceptor than clonidine. In addition, dexmedetomidine is shorter-acting drug than clonidine and has a reversal drug for its sedative effect, atipamezole. These properties render dexmedetomidine suitable for sedation and analgesia during the whole perioperative period: as premedication, as an anesthetic adjunct for general and regional anesthesia, and as postoperative sedative and analgesic.

Alpha2-receptors are found in many sites throughout the body. Alpha2-adrenoceptors are found in peripheral and central nervous systems, in effector organs such as the liver, kidney, pancreas, eye, vascular smooth muscles and platelets. Alpha2-adrenoceptors are divided into three subthypes: the *subtype a*, the predominant subtype in central nervous system, is responsible for the sedative, analgesic and sympatholytic effect; the *subtype b,* found mainly in the peripheral vasculature, is responsible for the short-term hypertensive response, and the *subtype c*, found in the central nervous system, is responsible for the anxiolytic effect.



Pharmacodynamics of dexmedetomidine

The highest densities of alpha2- receptors are found in the locus ceruleus, the predominant noradrenergic nuclei of the brainstem and an important modulator of vigilance. Presynaptic activation of the alpha2-a adrenoceptor in the locus ceruleus inhibits the release of norepinephrine and results in the sedative and hypnotic effects in addition, the locus ceruleus is the site of origin for the descending medullospinal noradrenergic pathway, known to be an important modulator of nociceptive neurotransmission.

Stimulation of the alpha2-adrenoceptors in this area terminates the propagation of pain signals leading to analgesia. Postsynaptic activation of alpha2-adrenoceptors in the CNS results in decrease in sympathetic activity leading to hypotension and bradycardia. At the spinal cord, stimulation of alpha2-receptors at the substantia gelatinosa of the dorsal horn leads to inhibition of the firing of nociceptive neurons and inhibition of the release of substance P. Also, the alpha2-adrenoceptors located at the nerve endings have a possible role in the analgesic mechanisms of alpha2-agonists by preventing noradrenaline release.

Pharmacokinetics of Dexmedetomidine

Dexmedetomidine, an imidazole compound, is the active d-isomer of medetomidine. Following intravenous administration, dexmedetomidine exhibits the following pharmacokinetic parameters: a rapid distribution phase with distribution half-life (t ½ α) of 6 minutes; elimination half-life (t ½ β) of 2 hours; volume of distribution (vss) 118 litres. Dexmedetomidine exhibits linear kinetics when infused in the dose range of 0.2-0.7 micrograms/kg/h for not more than 24 hours. Dexmedetomidine undergoes almost complete biotransformation through direct glucuronidation and cytochrome p450 metabolism. Metabolites of biotransformation are excreted in the urine (95%) and feaces. The average protein binding of

dexmedetomidine is 94%. Dexmedetomidine is a white powder that is freely soluble in water and pKa of 7.1.

Dosage

It is supplied as 100 µg/ml, 2 ml vial which must be diluted with 48 ml of 0.9% sodium chloride solution prior to administration. For adult patient, dexmedetomidine is administered by a loading infusion of 0.5-1 µg/kg over 10 minutes, followed by a maintenance infusion of 0.2 to 0.7 µg/kg/hr. The effect appears in 5-10 minutes, and is reduced in 30-60 minutes. The maintenance infusion is adjusted to achieve the desired level of sedation.

Perioperative uses of dexmedetomidine

i) Premedication

Dexmedetomidine possesses anxiolytic, sedative, analgesic, antisialogogue and sympatholytic properties. Intramuscular dexmedetomidine at a dose of 1 µg/kg is used for premedication.

ii) Intraoperative uses of dexmedetomidine

Intraoperative uses of dexmedetomidine include its use as adjunct to general anesthesia, as adjunct to regional anesthesia, in monitored anesthesia care (MAC), or as a sole agent for total intravenous anesthesia (TIVA).

iii) Use of dexmedetomidine in the postoperative period

Dexmedetomidine's special properties favour its use in the recovery room. In addition to its sympatholytic effects, analgesic effects, decreased rate of shivering and the preservation of respiratory function allows the continuation of the dexmedetomidine infusion in the extubated, spontaneously breathing patient. The possibility of ongoing sedation and sympathetic block could be beneficial in reducing high rates of early postoperative ischemic events in high-risk patients undergoing non-cardiac surgery.

Contraindication

i) Pre-existent severe bradycardia and conduction problems.
ii) In patients with reduced ventricular functions (ejection fraction<30%)
iii) In patients who are hypovolemic or hypotensive.

Adverse effects

The common adverse effects of dexmedetomidine include hypotension, hypertension, nausea, bradycardia, atrial fibrillation, hypoxia and various atrioventricular blocks.

ASSESSMENT OF BLOCKADE AFTER SPINAL ANAESTHESIA

Following subarachnoid block assessment of motor & sensory block is done in the following manner.

SENSORY BLOCK

Sensory block was assessed by loss of sensation to pinprick using 23G sterile needle. The assessment was started immediately after injection and continued every 30 secs till loss of pinprick sensation at T10 level. Onset of sensory block was taken as time from intrathecal injection to loss of pinprick sensation atT10. At regular interval after SAB , the dermatomal level of sensory block was assessed till a maximum level of sensory block was attained.

MOTOR BLOCK

Motor block was assessed using modified BROMAGE score: The motor block was assessed according to the modified Bromage scale (8):

1. Bromage 0 - the patient is able to move the hip, knee and ankle
2. Bromage 1 - the patient is unable to move the hip but is able to move the knee and ankle
3. Bromage 2 - the patient is unable to move the hip and knee but able to move the ankle

4. Bromage 3 - the patient is unable to move the hip, knee and ankle.

Assessment of motor block was started immediately after the intrathecal injection. It was tested every min till BROMAGE SCORE of 3 was reached. Onset of motor block was taken as time taken to achieve BROMAGE score of 3 from Subarachnoid block. The degree of motor block after 20mins of injection was noted and this was considered maximum degree of motor block. Thereafter motor block regression was noted and duration of motor block was taken as time from SA injection to return of BROMAGE score to 0

ASSESMENT OF SEDATION AND PAIN:

Sedation was assessed using **Ramsay sedation score** and pain was assessed using **visual analogue scale**:

Ramsay Sedation Score :

1 Anxious, agitated or restless

2 Co-operative, oriented, tranquil but alert

3 Responds to command

4 Asleep but brisk response to glabellar tap or loud auditory stimuli

5 Asleep, sluggish response to glabellar tap or auditory stimuli

6 Asleep, no sleep response

REVIEW OF LITERATURE

Clonidine combined with local anaesthetics in spinal anaesthesia

Van tuijl *et al.,* [34] investigated the effect of addition of clonidine to hyperbaric bupivacaine on post operative morphine consumption after caessarian section.

A group of 106 patients were randomly allocated to receive spinal anaesthesia with either 2.2 ml of 0.5% bupivacaine heavy with 0.5ml NS 0.9% total 2.7 ml (Gp B) or to receive 2.2 ml of 0.5% bupivacaine heavy with clonidine 0.5 m1-75 μg diluted in 0.9% NS total of 2.7 ml (Gp BC). The time for first analgesic request was 129 mins in the BC gp compared to 55 mins in the B gp. In the BC gp 58% had a MAP <70 mmHg compared to 9% in gp B. Clonidin added to bupivacaine in caessarian section prolongs the duration of analgesia and motor block. It did not result in reduced morphine consumption in the first post operative day.

Wu *et a1.,*[32] studied the effect of adding clonidine to hyperbaric tetracaine spinal anaesthesia in 60 ASA class I - II patients .The subjects were randomly allotted to 4 groups. All patients received tetracaine 10 mg in 10% glucose solution 2 ml. Patients in group I received the above medication and were the control group, patients in other group received tetracaine plus increasing doses of clonidine: 15 μg (gp 2) ,30 μg (gp 3) and 45 μg (gp 4). The three clonidine groups had significant increase in sensory

regression time to L1 level (by 42 ,47 , 60%, respectively) and also had significantly increased motor complete recovery time, but the incidence of hypotension and bradycardia was increased in clonidine 45 µg group. He concluded that addition of l5 µg or 30 µg may be useful as a means of increasing the duration of hyperbaric tetracaine spinal anaesthesia.

Niemi studied the analgesic and circulatory effects of intrathecal clonidine in patients undergoing knee arthroscopy under spinal anaesthesia. Forty ASA I and II patients were randomly divided into 2 group. One group received clonidine 3µg/kg mixed with 0.5% bupivacaine and the other group an identical saline volume mixed with bupivacaine as above in a double blinded fashion. Oxycodone 0.14 mg/kg i.m or ketoprofen 100 mg p.o was administered when needed. The duration of sensory analgesia, was longer in clonidine group (mean 215 mins) than in control group (mean 160 mins) ($p<0.05$). Duration of motor blockade was also longer in clonidine group (mean 161 mins) ($p<0.05$). Mean arterial pressure and heart rate were significantly lower in the clonidine group compared to control group. More patients in the clonidine group were sedated 3-6 hrs after the injection ($p<0.05$). Addition of clonidine prolonged the bupivacaine spinal block.

De Negri *et al.,* studied to determine whether intrathecal administration of clonidine can reduce the dose of local anesthetic, and the effects of clonidine on cardiovascular system and on arousal level. In 56

patients scheduled for minor surgical procedure (spermatic vein ligature) under unilateral spinal anesthesia with hyperbaric bupivacaine 1% one half of patients received clonidine 150 μg in addition to bupivacaine. Cardiac output, stroke volume, ejection fraction were measured by thoracic electric bio impedance method, baseline and until 1 h after surgery. In clonidine treated group, variations of cardiovascular parameters were observed, in the same group sensory block, motor block were significantly prolonged. A higher sedation level and a significant post operative analgesia were also observed. The addition of clonidine to hyperbaric bupivacaine seems to be particularly useful in unilateral spinal anesthesia, exerting minimal influence on hernodynamic parameters and guaranteeing a satisfactory postoperative analgesia.

Seah *et al.,* studied the prolongation of analgesic effect of hyperbaric bupivacaine spinal anesthesia with clonidine. 40 AS A class I & II patients scheduled for TTJRP were randomly classified into 2 groups of 20 each. In the saline group, 3 m1 of 0.5% hyperbaric bupivacaine + 1ml NS was given. In the clonidine group, 1ml of (150 μg) clonidine in addition to 3 ml of 0.5% bupivacaine was given. The mean time for two segment regression to L2 was significantly greater in clonidine group than in the saline group. Motor block was also prolonged in the clonidine group than in the saline group. Side effects such as hypotension and bradycardia commonly

occurred in clonidine group, but all patients could be effectively treated with ephedrine and atropine, respectively.

Clonidine as sole analgesic in spinal anaesthesia

Fibs kritonl *et al.* [4] studied to evaluate the effect of intrathecal clonidine as the sole analgesic on pain following caessarian section. Twenty patients who underwent elective caessarian section receive 45 mins after GA either 150 µg clonidine (n=10) or saline (n=10) intrathecally. Pain scores were lower in clonidine than saline treated patients. Pain relief in terms of the first supplemental analgesic requested by patients lasted 414 mins after clonidine and 181 mins after saline. The results suggest that 150 µg clonidine is effective in pain following caessarian section but is not free of side effects like hypotension, sedation and dryness of mouth.

Goudas Leonidas *et al.* [19] studied to evaluate the dose response hemodynamics and analgesic profiles of intrathecal clonidine. 30 women who underwent LSCS under GA 45 mins after tracheal extubation, a lumbar puncture was performed and patients received 150 µg (gp 1) ,300µg 2) and 450µg (gp 3) clonidine. Pain relief lasted 402 ±75 mins in group 1,570+ 76 mins in gp 2, 864± 80 mins in gp 3 . Sedation was found in all three groups. The results demonstrated dose dependent analgesia after intrathecal clonidine at doses as great as 450 µg .A relative hemodynamic stability is suggesting a pressor effect at peripheral sites.

Clonidine combined with opioids and local anesthetics in spinal anesthesia

Chiari astrid *et al.*[7] evaluated the dose response potency of intrathecally administered Clonidine during 1st stage of labour along with Sufentanil. 36 parturients received 50 µg, 100 µg and 200 µg of intrathecal clonidine.

The duration of analgesia was significantly more in 200 µg gp. Duration and quality of analgesia were more pronounced in 100 µg, 200 µg than with 50 µg. The high incidence of hypotension requires caution with use of 200 µg for labour analgesia.

Gautier Philippe *et al.*[20] studied the efficacy of low doses of intrathecal Clonidine (15 µg & 30 µg) combined with sufentanil. 93 parturients received one of the following intrathecal solutions, either 15 µg clonidine (n=10), 30 µg clonidine (n=10), 2.5 µg sufentanil and 15 µg clonidine (n=13), and 5 µg sufentanil with 30 µg clonidine (n=13). Patients receiving 30 µg intrathecal clonidine with 2.5 or 5 µg sufentanil had significantly long lasting analgesia. 30 µg intrathecal clonidine with 2.5 or 5 µg intrathecal sufentanil had significantly increased the duration of analgesia during the first stage of labour without adverse maternal or fetal effects.

Benhamou Dan *et a1*.[2] studied 78 pregnant women at term scheduled for, elective caessarian section to compare the analgesic efficacy and side effect profile of a spinal block with hyperbaric bupivacaine alone (group B) or combined with 75 μg clonidine (group BC) or with clonidine 75 μg and fentanyl 12.5 μg (group BCF). Adding a small dose of intrathecal clonidine to bupivacaine increases the quality of intraoperative analgesia and decreases pain during cesarian section. Combining clonidine with fentanyl further improved analgesia.

Acalovschi lurie *et al.*[1] studied the effects of intrathecally administered epinephrine and clonidine on the duration and quality of meperidine spinal block. 45 patients scheduled for orthopaedic surgery divided into 3 groups, received spinal anaesthesia with 1 mg/kg meperidine 5% alone or with 200 μg epinephrine or 2 μg/kg clonidine.

The duration and degree of motor block were increased by addition of both epinephrine and clonidine. A tendency toward bradycardia and decrease in MAP was potentiated by clonidine. The co administration of clonidine or epinephrine with meperidine enhances the duration and degree of spinal anaesthesia and that adding clonidine prolongs duration of post operative analgesia.

Owen *et al.*[30] studied to determine whether the addition of clonidine and neostigmine to intrathecal bupivacine fentanyl would increase the

duration of analgesia without increasing side effects for patients in labour. 45 healthy parturients in active labour received 2 m1 intrathecal dose of one of the following dextrose containing solutions: 1. Bupivacaine 2.5 mg and fentanyl 25 μg (BF) 2. BF + Clonidine 30 μg 3. BFC + neostigmine 10 μg (BFCN). Patients administered BFCN had significantly longer analgesia (165 + 32 mins) than those who received BF (90 +21 mins) or BFC (123±21 mins) $p<0.001$. The addition of clonidine and neostigmine significantly increased the duration of analgesia but neostigmine caused more nausea.

Dexmedetomidine compared with Clonidine/opioids and local anesthetics in spinal anesthesia

Intravenous Dexmedetoniidine vs. Intravenous Clonidine to prolong Bupivacaine Spinal Anesthesia. A Double Blind Study by Victor 'Whizar *et al.* – intravenous Dexmedetomidine as well as intravenous clonidine given after spinal bupivacaine anesthesia was able to prolong anesthesia compared to placebo. Initial dexmedetomidine mean dose was 70±7.5 μg, and mean maintenance dose 34+4 μg/kg/h. Clonidine mean dose was 268±32 μg. Sensory block duration was longer in D and C groups, 208±43.5 and 225±58.8 min respectively, vs. placebo group 137±121.9 min (P=0.05). Motor block duration was longer in Group D and C (191±49.8 and 172±36.4) vs. placebo group (172±36.4) without significant statistical

difference. Hemodynamic changes (bradycardia, hypotension) were similar in all groups and without clinical relevance.

Effect of Adding Dexmedetomidine vs. Fentanyl to Intrathecal Bupivacaine on Spinal Block Characteristics in gynecological Procedures: A Double Blind Controlled Study- Subhi M. Al-Ghanem *et al.* studied 76 patients scheduled for vaginal hysterectomy. They receive intrathecally either 10 mg isobaric bupivacaine plus 5 μg dexmetedomidine (group D, n=38) or 10 mg isobaric bupivacaine + 25 μg fentanyl (group F, n=38), the onset time to reach peak sensory and motor level, the regression time for sensory and motor block, hemodynamic changes and side effects were recorded. 5 μg dexmetedomidine produces prolonged motor and sensory block compared with 25 μg fentanyl. Patients in group D had significant longer sensory and motor block. The mean time of sensory regression to S1 was 274±73 min in group D and 179±47 min in F ($P < 0.00\ 1$). The regression time of motor block to reach modified Bromage 0 was 240±60 min in D and 155+46 min in F ($P < 0.00\ 1$). The onset times to reach 110 dermatorne and to reach peak sensory as well as onset time to reach modified Bromage 3 motor block were not significantly different between the two groups.

Effect of dexmedetomidine added to spinal bupivacaine for urological procedures - Mahmoud M. Al-Mustafa *et al.* - Dexmedetomidine has a dose

dependant effect on the onset and regression of sensory and motor block when used as an adjuvant to bupivacaine in spinal anesthesia. Sixty-six patients were into 3 groups, each receiving spinal bupivacaine 12.5 mg combined with normal saline (group N), Dexmedetomidine 5 μg (group D5), or dexmedetomidine 10 μg (group D10). The onset times to reach T10 sensory and Bromage 3 motor block, and the regression times to reach S1 sensory level and Bromage 0 motor scale, were recorded: The mean time of sensor block to reach the T10 dermatome was 4.7±2.0 mins in D10 group, 6.3±2.7 mins in D5, and 9.5±3.0 mins in group N. The mean time to reach Brornage 3 scale was 10.4±3.4 mins in group Dl0, 13.0±3.4 mins in D5 and 18.0±3.3 mins in group N. The regression time to reach S1 dermatome was 338.9+44.8 mins in group D10, 277.1+23.2 mins in D5 and 165.5+32.9 mins in group N. The regression to Bromage 0 was 302.9±36.7 mins 246±25 mins in D5 and 140±32 mins in N.

Effect of low-dose dexmedetomidine or clonidine on the characteristics of bupivacaine spinal block by Kanazi et al. - Dexmedetomidine (3 μg) or clonidine (30 μg), when added to intrathecal bupivacaine, produces a similar prolongation in the duration of the motor and sensory block with preserved hemodynamic stability and lack of sedation. 60 patients undergoing transurethral resection of prostate or bladder tumor under spinal anesthesia were randomly allocated to one of

three groups. Group B received 12 mg of hyperbaric bupivacaine, D received 12 mg of bupivacaine supplemented with 3 μg of dexmedetomidine and group C received 12 mg of bupivacaine supplemented with 30 μg of clonidine. Patients in groups D and C had a significantly shorter onset time of motor block and significantly longer sensory and motor regression times than patients in B. The mean time of sensory regression to the S1 segment was 303±75 min in group D, 272±38 min in C and 190±48 min in group B (B vs. D and B vs. C, $P < 0.001$). The regression of motor block to Bromage 0 was 250 ±76 min in group D, 216±35 mm in group C and 163 ± 47 min in group B (B vs. D and B vs. C, $P < 0.00$ 1). The onset and regression times were not significantly different between groups D and C. The MAP, heart rate and level of sedation were similar in the three groups intra-operatively and post operatively.

MATERIALS AND METHODS

This study was conducted at Madurai Medical College Hospital, Madurai between March 2011 to August 2011 on 94 patients of ASA physical status I, II and III undergoing infra umbilical surgeries.

This study was done after Ethical Committee approval and written informed consent obtained from all patients included in the study.

STUDY DESIGN

This study was done in a prospective double blinded randomized manner.

SELECTION OF CASES

Inclusion criteria

- Patients in age group of 18 to 70 yrs
- ASA - PS I, II and III
- Infra umbilical surgeries

Exclusion criteria

- ASA - PS IV
- Patient refusal
- Renal/ hepatic disfunction
- Allergic to the drugs

- Contra indication to subarachnoid block
- Labile hypertension, arrhythmias, currently on anti hypertensive therapy

94 patients were included in this double blinded randomized controlled study.

Patients were divided into 3 groups.

Patients in **group B** received 2.5ml of 0.5% hyperbaric bupivacaine plus 0.5ml preservative free normal saline.

Patients in **group C** received 2.5ml of hyperbaric bupivacaine with 50 µg of clonidine in 0.5 ml preservative free normal saline.

Patients in **group D** received 2.5ml of hyperbaric bupivacaine with5µg of dexmedetomidine in 0.5 ml preservative free normal saline.

Pre Anaesthetic Evaluation

Patients included in the study underwent thorough pre operative evaluation which included the following

History

History of underlying medical illness, previous surgery, anesthesia and hospitalization.

Physical examination

1. GC of the patient

2. Vital signs

3. Height and weight

4. Examination of CVS, RS, CNS and vertebral columns

5. Airway assessment

Investigations

Hb, PCV, BT, CT, RFT, blood sugar, ECG, CXR, platelet count, blood grouping and cross matching were done. Patients who satisfied the inclusion criteria were explained about the nature of the study and the anesthetic procedure. Written informed consent was obtained from all patients included in the study.

HOW DOUBLE BLINDING WAS DONE

Allotment of cases was done by table of random numbers. The Consultant who made the drug combination took no further part in the study. I performed the subarachnoid block and noted the observations both intra-operatively and post-operatively.

Technique

In the OT, appropriate equipment for airway management and emergency drugs were kept ready. No premedication were given prior to the surgery. The horizontal position of the operating table was checked and patient shifted to the table. I.V. line was secured and preloaded with 500 ml Ringer lactate solution. NIBP, Sp02 were connected to the patient.

Preoperative baseline systolic and diastolic BP, PR, Sp02 and RR were recorded. SAB was done and observations were made in all the patients involved in the study. Under strict aseptic precautions a midline lumbar puncture was performed using a 24/25G Quincke needle in sitting position/right lateral decubitus position. The patient was then immediately placed in supine position. Lumbar puncture was successful in first attempt in almost all the patients. Vital signs were recorded at 5 mins interval intraoperativel until the end of surgery. In the recovery room vital signs were recorded every 15 mins. The sensory block level was assessed by pinprick sensation using a 25 guage needle along the midclavicular line bilaterally. The motor block was assessed according to the modified Bromage scale (8): Bromage 0, the patient is able to move the hip, knee and ankle; Bromage 1 the patient is unable to move the hip but is able to move the knee and ankle; Bromage 2, the patient is unable to move the hip and knee but able to move the ankle; Bromage 3, the patient is unable to move the hip, knee and ankle. The times to reach T10 dermatorne sensory block peak sensory level and Bromage 3 motor block were recorded during surgery. The regression time for sensory and motor block were recorded in recovery room. All durations were calculated considering the time of spinal injection as time zero. Patients were discharged from the recovery room after sensory regression to S1 dermatome and Bromage 0 was attained.

Assessment of pain intra-operatively was done using visual analogue pain scale between 0-10 (0 = no pain, 10 = the most severe pain).

Intraoperative nausea, vomiting, pruritus, additive analgesia and sedation were recorded. T1 sedation was assessed using Ramsay Sedation Score.

1 Anxious, agitated or restless

2 Co-operative, oriented, tranquil but alert

3 Responds to command

4 Asleep but brisk response to glabellar tap or loud auditory stimuli

5 Asleep, sluggish response to glabellar tap or auditory stimuli

6 Asleep, no sleep response

The time for intrathecal injection was considered as 0 and the following parameters were observed - sensory blockade and motor blockade, duration of analgesia and sedation.

Vital signs and side effects

The PR, systolic and diastolic BP, Sp02 and RR were recorded for every 5 mins till one hour and then every 10 mins throughout the intra operative period.

Hypotension defined as fall in systolic BP > 30% from baseline or SBP < 90 mmHg. This was managed with inj. Ephedrine 6 mg and a bolus

administration of 250 ml of RL solution over 10 mins. The above was repeated if BP remained low.

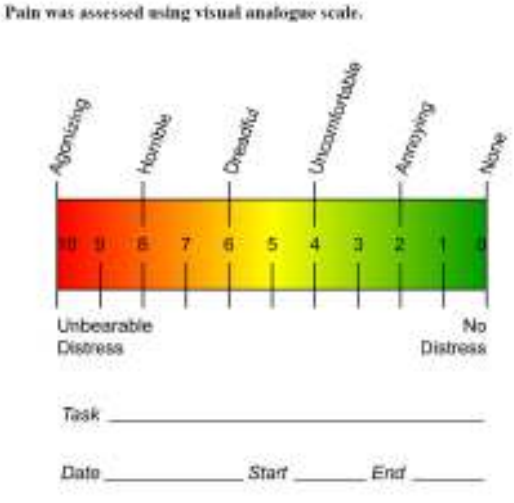
Bradycardia was defined as HR < 50/min and this was managed with inj. atropine 0.3 to 0.6 mg i.v.

Respiratory depression defined as RR< 8/min and or Sp02 < 85%. This was planned to be managed with bag and mask ventilation or intubation and IPPV if necessary. Blood loss more than the allowable loss was replaced with blood.

Assessment in Recovery Room

Patient was shifted to recovery room after completion of surgery, the vital signs, sensory and motor blockade assessment were recorded, every 15 mins till a Bromage 0 and a sensory regression to S1 dermatorne was obtained. After the above were attained, the patients were shifted to post operative ward.

Assessment of pain and duration of analgesia



In the recovery room pain assessment using VAS were done every 15 mins. At the end of surgery, the degree of pain was assessed using VAS scale till VAS score >/= 4 was reached. Whenever the patient

complained of pain a rescue analgesic (Inj. Diclofenac 75 mg i.m) was given. Duration of effective analgesia was defined as time interval between onset of SAB and the time to reach VAS >/=4.

Patients were monitored for 24 hrs to detect the occurence of side effects - respiratory depression, nausea, vomiting, dry mouth and pruritis. Patients were also enquired about the occurence of Transient neurological symptoms which was described as pain / paresthesia in the neck, buttocks, legs or pain radiating to lower extremities after initial recovery from SAB within 72 hrs.

OBSERVATIONS & RESULTS

Statistical analysis

All recorded data were entered using MS Excel software and analysed using SPSS ver.16 software for determining the statistical significance.

Results are expressed as the means and standard deviations, medians and ranges, or numbers and percentages. The comparison of normally distributed continuous variables between the groups were performed using one-way Analysis of variance (ANOVA) and, if appropriate, followed by the Bonferroni's test for post hoc analysis. Nominal categorical data between study groups were compared using the chi-squared test or Fisher's exact test as appropriate. Ordinal categorical variables and non-normally distributed continuous variables were compared using Mann—Whitney U-test. $P < 0.05$ was considered to be significant.

DEMOGRAPHICS

Table 1
Demography

		N	Mean	Std. Deviation	F	Sig.
Age (yrs)	Bupivacaine	33	42.85	9.856	.35	P<0.70
	Clonidine	33	41.21	8.749		
	Dexmedetomedine	28	43.29	12.186		
	Total	94	42.40	10.183		
Weight(kg)	Bupivacaine	33	55.67	8.061	0.427	P<0.654
	Clonidine	33	54.00	7.331		
	Dexmedetomedine	28	55.82	10.760		
	Total	94	55.13	8.670		
Height(cms)	Bupivacaine	33	160.70	5.817	2.146	P<0.123
	Clonidine	33	158.45	7.045		
	Dexmedetomedine	28	161.86	6.824		
	Total	94	160.26	6.651		

One way ANOVA and t test shows no significant difference among the all three groups in terms of demography variable like Age, Height and Weight. (Suggesting comparability between the groups)

Table 2: ASA Physical Status Among The Groups

	ASA status			
	ASA 1	**ASA 2**	**ASA 3**	**Total**
Bupivacaine	24	9	0	33
	72.7%	27.3%	.0%	100.0%
Clonidine	21	12	0	33
	63.6%	36.4%	.0%	100.0%
Dexmedetomedine	17	10	1	28
	60.7%	35.7%	3.6%	100.0%
Total	62	31	1	94
	66.0%	33.0%	1.1%	100.0%

Pearsons chi(X^2) square test : $p<0.532$. All three groups are comparable by ASA Status

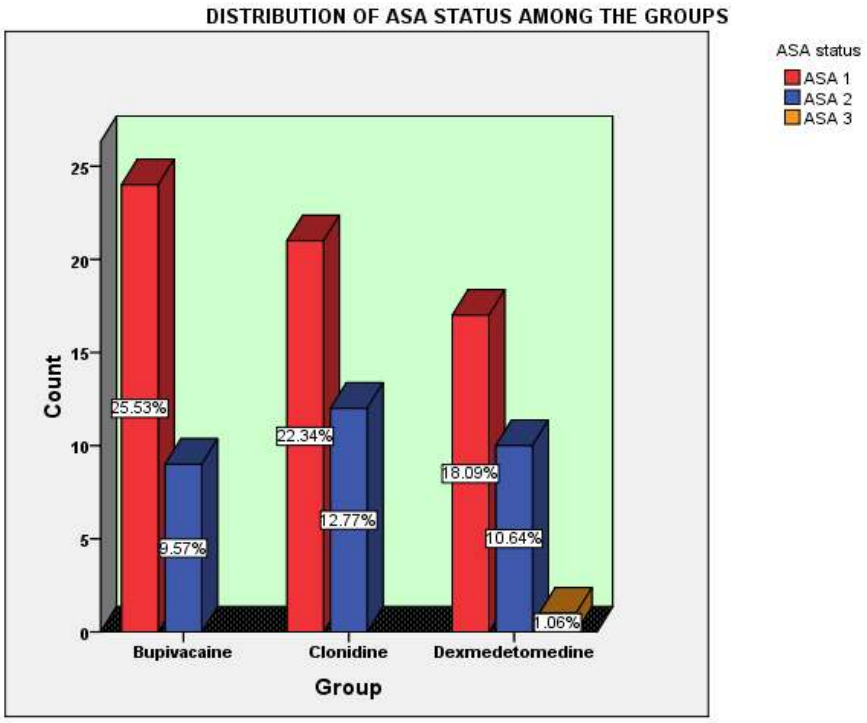
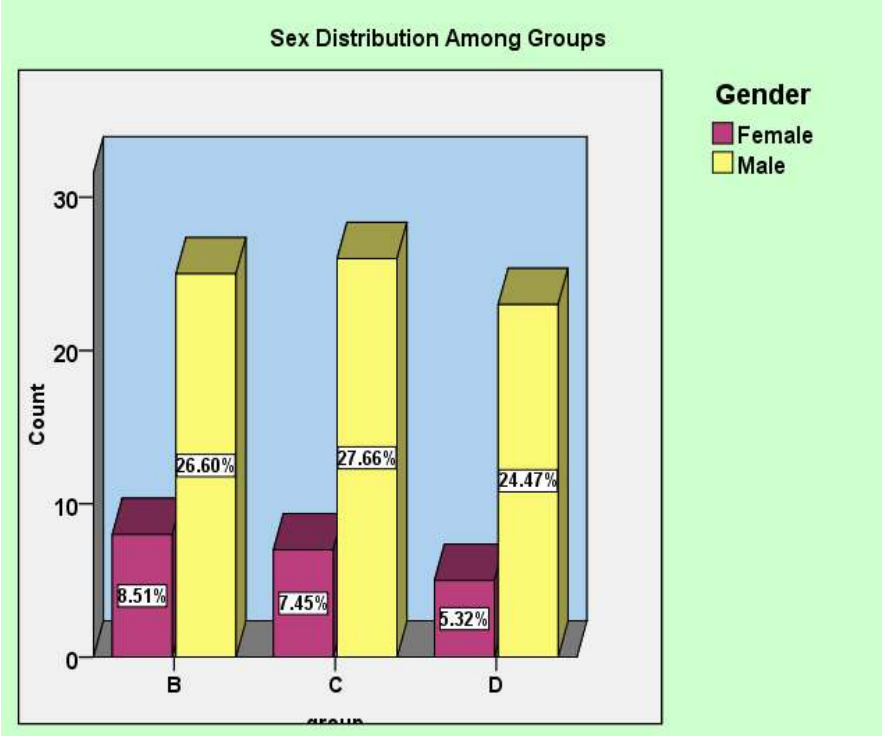


Table 3: Sex Distribution Among Groups

		Gender		
		Female	**Male**	**Total**
group	**B**	8 24.2%	25 75.8%	33 100.0%
	C	7 21.2%	26 78.8%	33 100.0%
	D	5 17.9%	23 82.1%	28 100.0%
Total		20 21.3%	74 78.7%	94 100.0%

Pearsons chi(X^2) square test: $p < 0.832$. The groups are comparable by sex distribution.



4. DURATION OF SURGERY

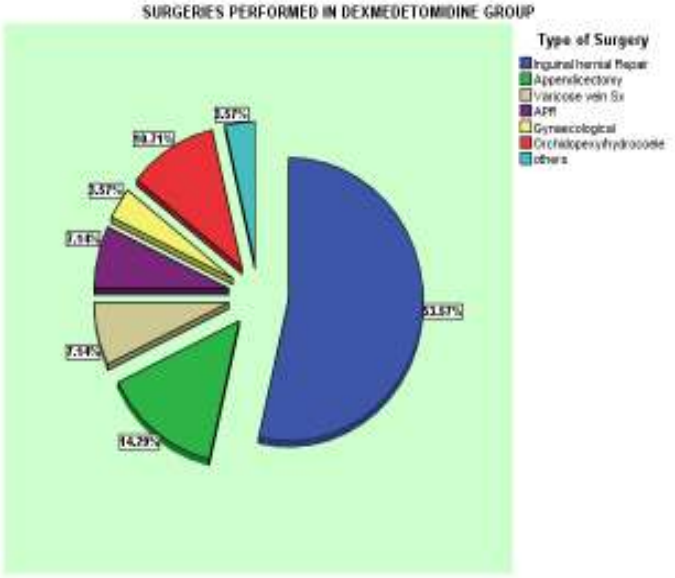
PARAMETERS	GROUP B	GROUP C	GROUP D	ANOVA
NO.OF CASES	33	33	28	
MEAN	91.7	100.8	91.9	P =0.37
S.D.	24.95	32.5	28.36	

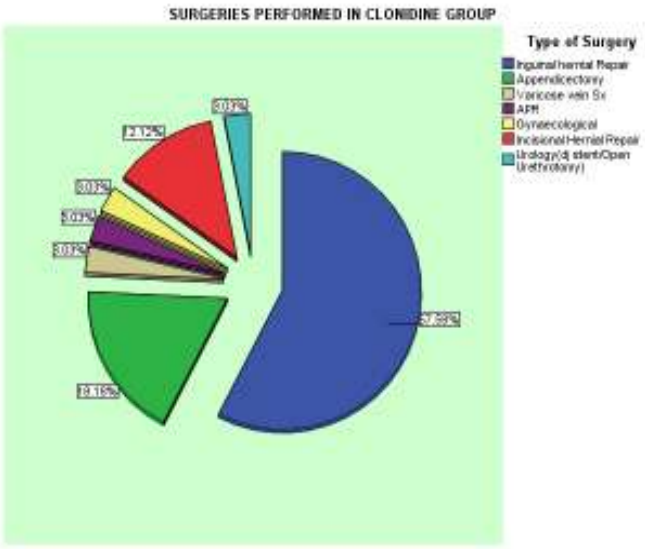
The mean duration of surgery is higher in Group C when compare to other two groups. But this is of no statistical significance.

5. TYPE OF SURGERY BY GROUPS

SURGERY	GROUP B	GROUP C	GROUP D
Inguinal hernial Repair	22 66.7%	19 57.6%	15 53.6%
Appendicectomy	0 .0%	6 18.2%	4 14.3%
Varicose vein Sx	0 .0%	1 3.0%	2 7.1%
APR	3 9.1%	1 3.0%	2 7.1%
Gynaecological	2 6.1%	1 3.0%	1 3.6%
Orchidopexy/hydrocoele	1 3.0%	0 .0%	3 10.7%
Incisional Hernial Repair	1 3.0%	4 12.1%	0 .0%
Urology(DJ stent/Open Urethrotomy)	3 9.1%	1 3.0%	0 .0%
others	1 3.0%	0 .0%	1 3.6%

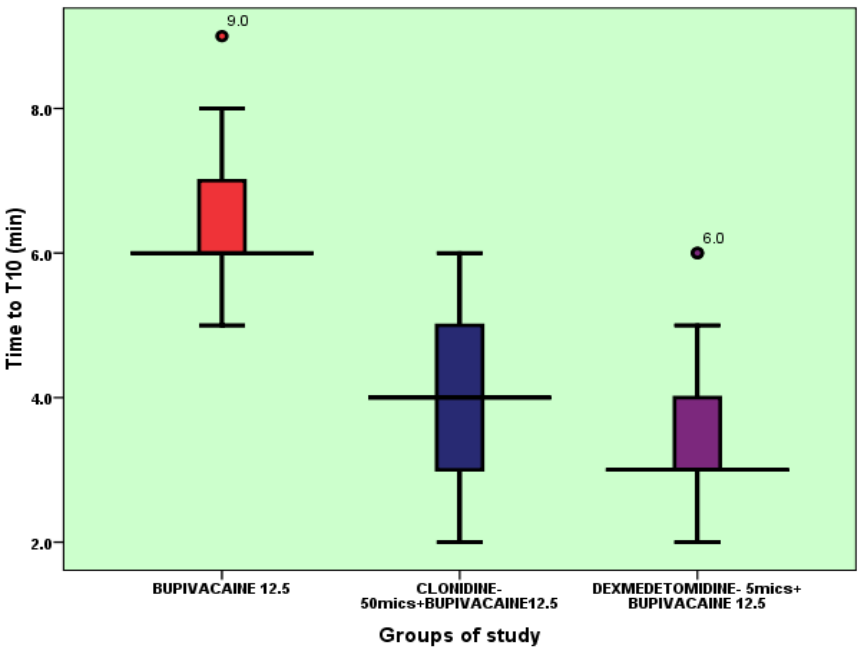
Pearsons CHI square test shows no significant difference in the surgeries performed between the study groups ($p<0.80$)





6. DISTRIBUTION OF MEAN ONSET OF SENSORY BLOCK (Mins) BY GROUPS

PARAMETERS	GROUP B	GROUP C	GROUP D	ANOVA
No. of cases	33	33	28	p-<0.0001
Mean	6.35	4.031	3.35	
S.D	10.809	43.542	32.23577	



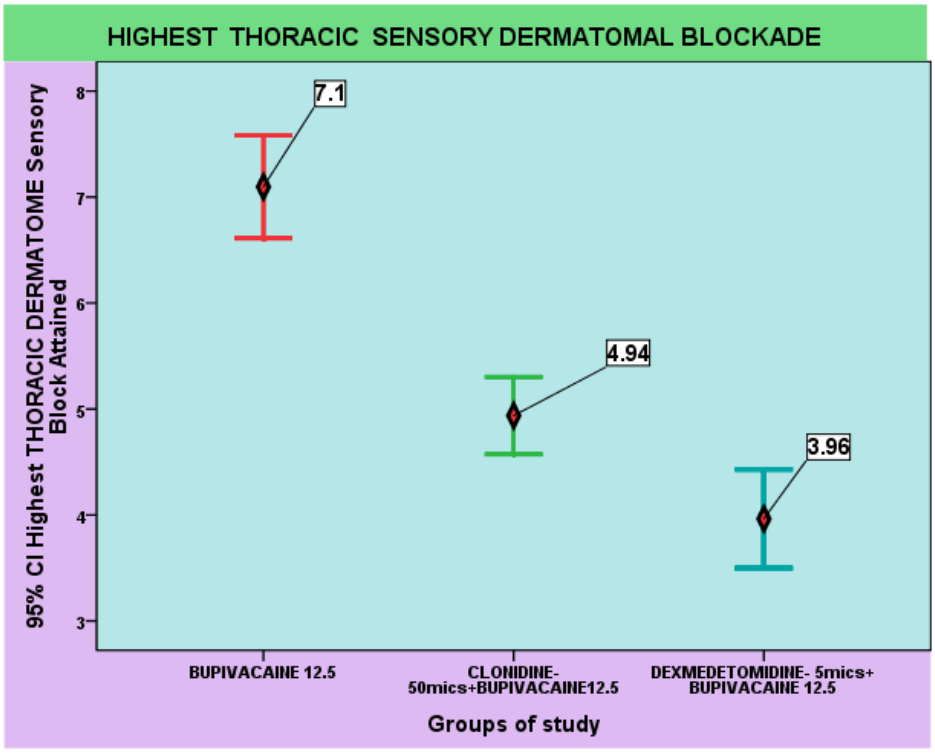
There is a significant difference between groups with regard to onset of sensory block with group D having a rapid onset compared to C. Both group C&D have significant early onset of sensory blockade than group B. The onset of sensory blockade is significantly faster for Dexmedetomidine than clonidine confirmed by Post Hoc test(bonferroni's test)

7. DISTRIBUTION OF MEAN ONSET OF MOTOR BLOCK (Mins) BY GROUPS

PARAMETERS	GROUP B	GROUP C	GROUP D	ANOVA
No. Of cases	33	33	28	<0.0001
Mean(min)	7.38	3.88	3.28	
S.D	1.251	1.040	1.1109	
Post Hoc Analysis(Bonferroni)		No difference between C&D(P>0.072)		

There is a shorter onset of motor block in group dexmedetomidine and clonidine Vs. bupivacaine group which is statistically significant. But post hoc analysis demonstrate no significant difference in the onset of motor blockade between dexmeditomidine and clonidine groups (bonferroni Post Hoc analysis- p >0.072).

8. DISTRIBUTION OF MAX. SENSORY BLOCK AMONG GROUPS



PARAMETERS	GROUP B		GROUP C		GROUP D	
	NO	%	NO	%	NO	%
T2	0	0	0	0	4	14.2
T3	0	0	2	6.6	5	17.9
T4	0	0	11	36.6	10	35.7
T5	4	13.2	6	19.8	6	21.5
T6	9	29.7	13	42.9	3	10.7
T7	7	23.1	2	6.6	0	0
T8	8	26.4	0	0	0	0
T9	4	13.2	0	0	0	0
T10	1	3.3	0	0	0	0
TOTAL	33	100	33	100	28	100

The median and range of the peak sensory level reached were T7 (T5–T10) in group B, T5 (T3–T7) in group C and T4 (T2–T6) in group D, with significant differences between the three groups even Clonidine and Dexmedetomidine(non parametric test- Kruskal Wallis rank test-*P* =0.002)

9. DISTRIBUTION OF CASE BY GROUPS AND GRADE OF MAXIMUM MOTOR BLOCK

PARAMETERS	GROUP B	GROUP C	GROUP D
No. Of cases	33	33	28
Mean	4	4	4
S.D	0	0	0

There is no difference between the groups in the grade of maximum motor block.

10. DISTRIBUTION OF MEAN TWO SEGMENTAL REGRESSION (mins) BY GROUPS

PARAMETERS	GROUP B	GROUP C	GROUP D	ANOVA
No. Of cases	33	33	28	P<0.001
Mean	77	99.53	136.55	
S.D	8.24	16.6	11.8	

There is a significant difference in the two segemental regression with Group D having a much prolonged duration of regression than B and C which of statistical significance both by ANOVA and Bonferroni test.

11. DISTRIBUTION OF MEAN DURATION OF MOTOR BLOCK (mins) BY GROUPS

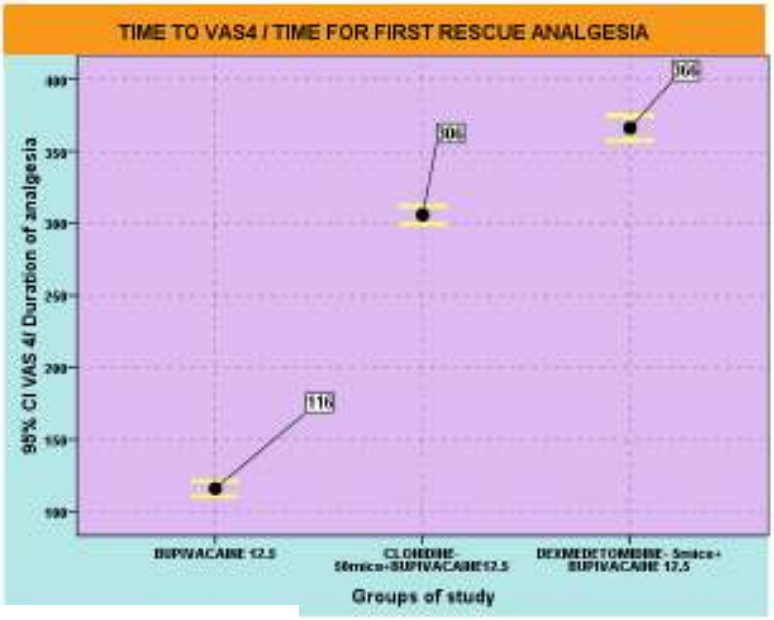
PARAMETERS	GROUP B	GROUP C	GROUP D	ANOVA
No. Of cases	33	33	28	P<0.0001
Mean	148.55	205.9	262.41	
S.D	13.848	12.904	16.693	

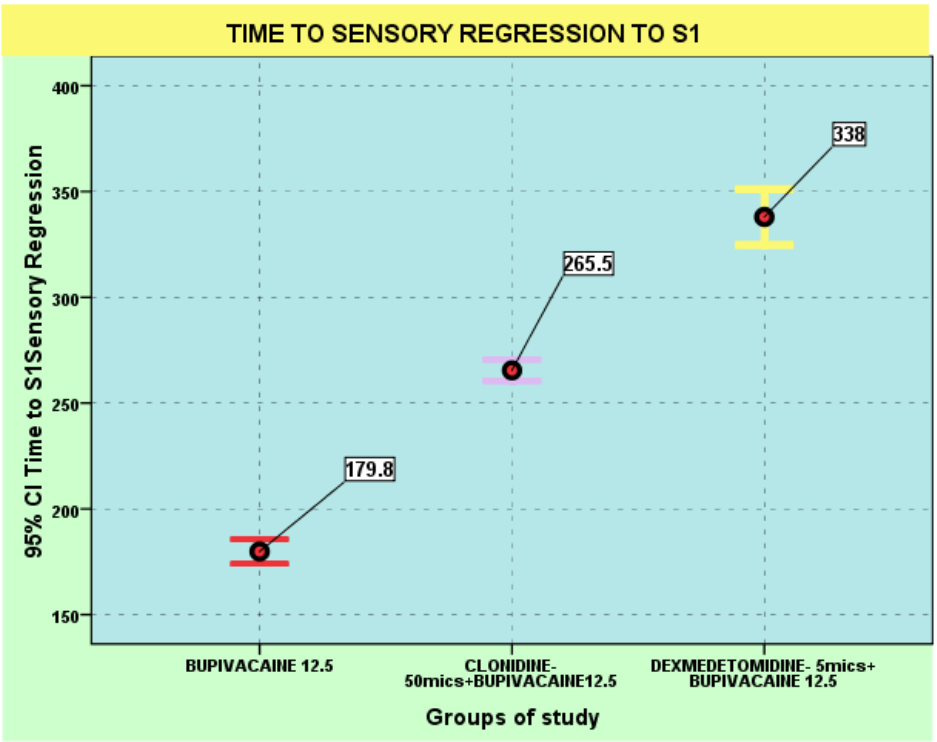
There is a significant difference between the groups interms of total duration of Motor blockade with Group D having much longer duration blockade than Group C and B. (By ANOVA and Bonferroni post hoc)

12 DISTRIBUTION OF MEAN DURATION OF ANALGESIA BY GROUPS

PARAMETERS	GROUP B	GROUP C	GROUP D	ANOVA
No. Of cases	33	33	28	P< 0.001
Mean	115.97	305.8	366.03	
S.D	9.215	17.341	28.635	

There is a significant difference between the groups interms of total duration of Analgesia with Group D having much longer duration than Group C and B





13 DISTRIBUTION OF MEAN DURATION OF SENSORY BLOCKADE BY GROUPS

Table:13 Total Duration Of Sensory Block(Time to S1 regression)

PARAMETERS	GROUP B	GROUP C	GROUP D	ANOVA
No. Of cases	33	33	28	P<0.0001
Mean	179.84	265.47	337.97	
S.D	14.22	17.28	22.45	

There is a significant difference between the groups in terms of total duration of Sensory Block with Group D having much longer duration than Group C and B (By ANOVA and Bonferroni post hoc - $p < 0.001$.)

14. DISTRIBUTION OF SIDE EFFECTS

EFFECTS	GROUP B		GROUP C		GROUP D	
	NO	%	NO	%	NO	%
HYPOTENSION	2	10	1	5	2	10
BRADYCARDIA	1	5	1	5	2	10
SEDATION	0	0	10	50	20	100
DRYNESS OF MOUTH	0	0	1	5	2	10

DISCUSSION

Alpha 2 agonist clonidine and dexmedetomidine, when added to local anaesthetics in sub-arachnoid block have shown to provide excellent surgical anaesthesia.

ONSET OF SENSORY BLOCK:

In my study, the mean time to onset of sensory block was 6.35 mins in group B and 4.03mins in group C and 3.35mins in group D. Both groups C&D have significant early onset of sensory blockade than group B, with Group D having a much rapid onset compared to group C.

Al-Mustafa et al[41,43] studied intrathecally administered 5µgms Dexmedetomidine combined with 0.5% Bupivacaine 12.5mg vs Bupivacaine 12.5mg alone. The sensory blockade onset time were 6.3 and 9.5mins respectively, which is similar to our study. But the delayed onset in sensory blockade in their study might have been due to SAB being performed in sitting position.

ONSET OF MOTOR BLOCK:

The mean time to onset of motor block was 7.3min in group B, 3.9 min group C and 3.3min in group D. The addition of dexmedetomidine and clonidine has significantly shortened the time to onset of motor blockade in

our study. Even though dexmedetomidine quickens the motor blockade than clonidine, it seems to be statistically insignificant (Post Hoc analysis doesn't show any significant difference between Group C&D (Bonferroni-p>O.072)).

Al mustafa et al[41,43] demonstrated similar findings in his study(Group B 8min, C-13 min, D-10 min). But the delayed onset in their study might be due to SAB being performed in sitting position.

MAXIMUM LEVEL OF SENSORY BLOCK:

There was a statistically significant difference among the groups in maximum level of sensory block. Median and range of Highest Sensory blockade attained were; Group B- T7 (T5-T1O), GroupC- T5 (T3-T7), GroupD- T4 (T2-T6).In our study, addition of dexmedetomidine has significantly increased the highest level of sensory blockade attained much more than even clonidine. Since dexmedetomidine has a higher sensory level of blockade (T2-T6) the possibility of dexmedetomidine used for supra umbilical abdominal surgeries should be explored.

Kanazi et a[40] in his study found that addition of intrathecal Clonidine 30 µgms and Dexmedetomidine 3 µgms to 0.75% Bupivacaine resulted in a much lower peak sensory levels in comparision to our study.(Group B T6(T4-10),group C T6.5(T3-9),group D T6(T 10)). This could be due to

lower dosage of Clonidine and Dexmedetomidine and lower volume of the drug administered used by Kanazi et al.[40]

MAXIMUM MOTOR BLOCK ATTAINED:

The median of maximum grade of motor block attained was grade 3 in all the groups measured using modified bromage scale. There is no statistically significant difference among the groups.

Klimscha et a1[23] showed that intrathecal clonidine 150 µgms added to 0.5% bupivacaine significantly increased the intensity of motor block.

Bonnet et al[3] in his study found that intensity and duration of motor block was prolonged with increasing the dose of clonidine from 75 mics to 150 mics added to 0.5% tetracaine 15mg.

TIME FOR TWO SEGMENTAL REGRESSION:

The mean time taken for two segmental regression was 99.53mins in group C compared to 136.55 mins in group D. Group D had significantly prolonged two segmental regression time compared to C&B(77mins).

This correlated well with the studies of Al-Mustafa et al[41,43] and Kanazi et al.[40]

MEAN DURATION OF MOTOR BLOCK:

The mean duration of motor block was 148.5mins in group B, compared to 205.9mins in group C & 262mins in Group D. Both ANOVA and Post Hoc test showed significant difference between the groups. Dexmedetomidine has a prolonged motor blockade, hence a longer post operative care unit admission and hence preventing an earlier discharge.

Kanazi et al[40] shows similar results(163, 216,250mins) respectively, Al Musthafa et al[41,43] demonstrated (140,246mins) in group B and D5 respectively. Which correlates with our study if we take the dosage and volume of the drugs in to consideration.

MEAN DURATION OF SENSORY BLOCKADE

The mean duration of sensory regression to first sacral dermatome was 179.8 mins in group B compared to 265.5 mins in group C & 338min Group D, which were statisticaly significant both by ANOVA and Bonferroni's Post Hoc analysis. Hence is produces prolonged periods of pain relief which correlates well with duration of analgesia. This correlated with study by kanazi et al[40]where there was significant prolongation of sensory blockade (190, 272, 303 mins in Group B,C,D respectively)

Dobrydnjov et al [11] also showed in his study that clonidine added to small dose bupivacaine for inguinal hernioraphy had prolonged analgesia compared to control group.

Gautier et al [20] showed in his study that clonidine combined with sufentanil for first stage of labour significantly prolonged analgesia compared with sufentanil alone.

Study by Mercier et a1 [27] showed addition of clonidine to intrathecal sufentanil for labour significantly prolonged analgesia.

Hemodynamic Characteristics

Both Clonidine and dexmeditomidine lowered the pulse rate,systolic BP, diastolic BP. But in clonidine lowering of Systolic BP was significant and sustained for a prolonged period. Hence higher dosages of clonidine should be used with caution in SAB. Hypotension was observed in 5-10% of patients in clonidine group. Hypotension was treated with ephedrine and bradycardia with Atropine.

Study by Chiari Astrid et a1[7] on analgesic and hemodynamic effects of intrathecal clonidine as a sole analgesic agent during first stage of labour showed hypotension was produced by increasing doses of clonidine.

Study by Fibs kriton et a1[14] found that hypotension is the main side effect.

Studies done by Freedman JM et a11[7] and J4ampl KF et a1[22] showed an increased occurrence of TNS in patients undergoing spinal anaesthesia with lignocaine.

Sedation

In our study patients in clonidine groups had deeper levels of sedation with RSS score 3.3 , which did not require any active intervention.

CONCLUSION

In conclusion the addition of Clonidine and Dexmedetomidine as adjuvants to bupivacaine in subarachnoid block, shortens the onset and prolongs the duration of both sensory and motor block.

We conclude that 5µgm of dexmedetomidine added to local anaesthetic in comparison to 50µgm of clonidine in subarachnoid block is more potent with respect to both onset and duration of sensory and motor blockade. Even though dexmedetomidine produced a lowering of heart rate and blood pressure they were not severe enough to warrant active intervention in most of the cases but the same cannot be said about higher dosages of clonidine.

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MASTER CHART

S. No.	group	name	age	sex	WT	HT	DmSx1	Rss2	2segreg1	TTlBlkDRnF	TimToBrZero	TtlDmAnal	timT0Hih	highestsensblk	timeT10	OrgBrmg3	MxSensBlk1
1	C	MADHAVAN	36	m	60	164	120	2	90	270	210	305	26	6	3	3	6
2	C	VENKATESAN	50	m	62	160	100	2	90	260	200	325	28	5	3.5	3	6
3	C	MOHANAVEL	46	m	54	156	65	2	75	240	190	325	30	4	3	3	4
4	C	ANJALATCHI	50	f	50	145	60	2	120	270	210	340	34	4	3	4	4
5	C	RAJA	36	m	56	158	120	3	100	265	200	320	20	5	3.5	4	4
6	C	SUNDER	40	M	68	156	60	3	110	250	205	310	28	4	4	5	4
7	C	LUND MARY	36	f	44	163	50	3	125	265	210	325	29	4	3	5	4
8	C	AGASAN	45	m	53	165	75	3	110	250	180	290	30	4	3	4	4
9	C	PADMANATHAN	45	m	62	142	70	2	120	270	200	325	24	6	6	4	6
10	C	VELU	40	m	55	166	150	4	125	250	210	285	25	6	5	2	6
11	C	ARAVIND	26	m	49	150	100	2	115	250	185	290	26	4	5	5	4
12	C	MANI	45	m	70	152	190	2	90	250	190	310	28	4	5	6	4
13	C	RAJESH	36	m	45	157	150	2	80	280	235	310	20	6	6	5	6
14	C	SUBRAMANI	46	m	57	174	90	2	85	285	220	295	24	6	4	4	6
15	C	RAVISHANKAR	26	m	54	154	75	2	85	280	210	310	23	6	4	4	6
16	C	NEELANKANDAN	21	m	45	158	100	3	110	270	220	310	28	4	6	3	4
17	C	RAMESH	24	m	50	169	90	3	125	250	215	300	28	6	4	3	6
18	C	GUNALAN	38	M	64	149	45	2	100	280	230	305	32	4	4	4	4
19	C	RAVI	39	m	44	154	135	2	120	260	190	305	28	5	5	3	6
20	C	AYYASWAMY	45	m	60	142	105	2	75	270	190	300	35	3	3	5	6
6	C	SELVARANI	30	f	55	164	120	2	100	275	215	305	21	5	2	2	
7	C	RAMAYEE	48	f	41	158	140	3	100	280	220	310	30	3	2	3	
10	C	FATHIMA	31	f	55	150	90	4	110	285	225	290	30	4	4	5	
11	C	KAKKAPPAN	51	m	52	164	100	3	110	280	220	325	15	6	5	4	
21	C	GANESAN	33	m	45	158	75	3	95	290	230	320	15	6	3	3	
29	C	GOVINDAMMAL	42	f	60	156	80	2	85	260	210	280	30	5	5	3	
30	C	MURUGESHWARAN	18	m	50	155	110	2	70	250	190	280	35	5	5	3	
31	C	GANESAN	51	m	56	158	120	2	100	245	180	265	27	6	3	4	
33	C	JEYAKUMAR	27	m	50	158	135	2	100	245	180	275	25	4	5	6	
34	C	MEGALA	18	f	45	150	115	3	80	280	200	320	26	6	5	5	
35	C	NIRMAL KUMAR	26	m	54	172	105	3	75	270	210	310	22	6	3	3	
39	C	SELVAM	45	m	65	160	85	2	85	270	210	320	26	6	4	4	
1	B	PARTHASARATHY	50	m	56	170	70	1	85	150	125	100	15	6	6	6	
2	B	VENU	28	m	45	164	100	1	80	180	150	130	19	7	7	7	
3	B	PARTAHASARATHY	50	m	60	172	45	1	70	190	160	120	22	6	7	7	
4	B	MALA	36	f	58	156	100	2	75	145	110	90	24	5	5	7	
5	B	PERUMAL	42	m	45	164	45	1	75	155	115	100	18	8	6	7	
6	B	RAMANI	36	f	56	161	120	2	80	200	170	130	14	9	7	9	
7	B	MAGALA	46	f	50	148	120	1	85	180	160	120	15	8	8	9	
8	B	SARATH	37	m	70	160	70	2	75	190	165	120	20	5	8	7	
9	B	VIJATSARATHI	20	m	40	158	60	2	70	200	165	120	23	6	5	5	
10	B	MADHAVAN	29	m	45	164	120	1	70	170	155	110	17	7	7	9	
11	B	RAJA	35	m	68	161	80	2	85	170	140	115	22	6	5	5	
12	B	MURUGAN	25	m	50	163	135	2	85	190	150	120	14	9	7	6	
13	B	NITHYANANDAM	22	m	58	156	120	2	80	180	145	110	16	8	6	5	
14	B	CHELLAMUTHU	50	m	70	154	105	2	80	180	135	100	18	7	5	6	
15	B	GUNASEKARAN	38	m	49	156	70	2	65	185	150	120	18	6	6	8	
16	B	KOKILA	45	m	69	166	80	1	70	180	155	100	22	6	6	6	
17	B	LOGONATHAN	38	m	54	165	90	2	70	185	150	125	19	7	7	9	
18	B	DEVBARARATH	22	m	49	162	130	2	75	200	145	145	16	9	6	7	
19	B	INIYAN	40	m	64	164	70	2	75	200	165	135	24	7	6	6	
20	B	MADHIVANI	36	f	50	168	130	2	80	165	125	110	18	10	5	7	
	B	SURESH	35	M	44	158	60	1	65	185	150	120	18	6	6	8	
	B	CHANDRAN	57	M	60	180	75	2	70	180	155	100	22	6	6	6	
	B	SENTHIL	39	m	60	160	70	2	75	160	135	110	18	8	6	7	
	B	PUGAZHENDHI	35	m	55	162	90	2	85	170	145	115	24	7	9	9	
	B	GOODFRED	41	m	60	155	85	2	80	175	145	120	22	6	6	6	
	B	SANTHOSAM	44	m	52	160	70	1	70	175	145	150	20	8	7	7	
	B	ESWARI	54	F	50	150	100	2	100	190	165	125	18	6	6	7	
	B	KUPPAN	32	m	60	165	120	2	80	190	165	120	22	5	6	6	
	B	GAYATHRI	56	F	55	160	110	2	80	150	110	90	24	6	5	6	

	B	SUDHA	27	f	65	170	100	2	75	190	160	95	15	7	7	8	
	B	KARI	53	m	65	160	90	1	75	200	175	120	18	9	5	8	
	B	PITCHAIAH	28	m	55	155	75	1	100	195	165	120	22	8	8	9	
	B	POTHUMPONNU	46	f	50	150	75	2	65	185	160	110	24	8	7	7	
40	D	VAIKUNDAM	40	m	54	165	150	2	145	310	240	340	15		2	3	5
32	D	SULOCHANA	43	f	62	164	70	2	140	360	280	380	23	3	3	3	4
36	D	ANANDHA KUMAR	18	m	47	163	100	3	135	400	310	410	23	2	3	4	3
1	D	MURUGAN	55	m	55	160	65	2	130	366	290	325	35	4	4	3	3
2	D	KANDHAN	60	m	67	158	75	2	140	275	220	330	15	5	2	3	2
3	D	PERIYASAMY	55	m	60	162	80	2	145	280	230	335	40	2	3	3	4
4	D	VELLAISAMY	42	m	70	168	145	2	135	330	270	380	12	6	3	2	5
5	D	PACHAI KANI	67	f	46	146	75	2	130	345	265	375	15	6	3	3	2
8	D	MARI	34	m	37	164	105	3	130	355	270	375	16	5	2	3	5
9	D	PALANI	68	m	53	168	120	2	145	380	280	380	15	2	2	3	2
12	D	VEERANNAN	52	m	46	160	140	2	145	335	250	365	21	3	3	3	4
13	D	DHARMARAJ	38	m	40	148	70	2	140	365	270	370	21	4	6	3	3
14	D	SUBRAMANI	43	m	58	170	90	2	140	345	260	380	24	4	3	3	5
15	D	ALAZHAR	60	m	39	156	105	2	155	360	270	390	21	3	3	3	5
16	D	MURUGAN	38	m	58	178	90	2	150	370	290	385	15	5	3	3	4
17	D	KALA	35	f	54	172	40	2	125	370	285	390	21	5	5	3	3
18	D	VANI	64	F	73	160	50	2	130	320	270	355	16	4	3	4	5
19	D	KARUPPAN	56	m	60	168	120	3	130	310	260	345	21	3	3	3	4
20	D	GNANAPANDITHAN	27	m	54	152	60	2	130	310	260	350	21	5	3	5	4
22	D	CHANDRASEKAR	45	m	60	156	90	2	110	280	230	340	16	4	6	5	5
23	D	SRINIVASAN	43	m	65	166	65	2	140	275	220	330	16	4	4	4	4
24	D	KASI VISHWANATHAN	54	m	66	162	60	2	125	290	250	345	24	4	5	3	2
25	D	SOUNDARAJAN	54	m	85	160	90	2	145	335	250	370	19	4	3	3	3
26	D	DULEEP	24	m	48	158	90	3	150	335	260	360	16	4	5	3	6
27	D	JEYAKUMAR	29	m	50	160	115	2	110	340	260	375	25	2	4	4	4
28	D	PETCHI AMMA	38	F	57	166	90	2	160	355	270	385	22	3	3	3	5
37	D	SARAVANAN	24	m	48	160	75	2	140	355	265	370	60	6	3	4	2
38	D	KARUPPIAH	40	m	55	165	120	3	140	360	265	380	15	4	2	3	4
43	D	CHINNAKALAI	65	m	50	162	120	2	120	390	270	400	30	5	3	3	5

S. No.	group	sex	age	wt	ht	ASA	Type of Sx	Sx type
1	D	M	55	55	160	I	B/L Varicose vein-	4
2	D	M	60	67	158	I	HERNIOPLASTY	1
3	D	M	55	60	162	I	HERNIOPLASTY	1
4	D	M	42	70	168	I	HYDROCOELE	6
5	D	f	67	46	146	III	CA SIGMOID- ANTERIOR RESECTION& ANASTOMOSIS	3
6	C	F	30	55	164	I	OVARIAN CYST	5
7	C	F	48	41	158	II	VAGINAL HYSTERECTOMY	5
8	D	M	34	37	164	I	ORCHIDOPEXY	6
9	D	m	68	53	168	II	HERNIOPLASTY-L	1
10	C	F	31	55	150	I	INCISIONAL HERNIA	7
11	C	M	51	52	164	I	B/L HERNIOPLASTY	1
12	D	M	52	46	160	I	B/L HERNIOPLASTY	1
13	D	M	38	40	148	II	HAEMORRHOIDECTOMY	9
14	D	M	43	58	170	I	HERNIOPLASTY-R	1
15	D	M	60	39	156	II	HERNIOPLASTY-R	1
16	D	m	38	58	178	II	HERNIOPLASTY-R	1
17	D	f	35	54	172	I	APPENDICULAR ABSCESS	2
18	D	F	64	73	160	I	VARICOSE	4
19	D	M	56	60	168	II	HERNIOPLASTY-R	1
20	D	M	27	54	152	I	HERNIOPLASTY-R	1
21	C	M	33	45	158	I	HERNIPLASTY-L	1
22	D	M	45	60	156	II	APR	3
23	D	M	43	65	166	I	INGUINAL HERNIA	1
24	D	M	54	66	162	II	HERNIPLASTY-R	1
25	D	M	54	85	160	I	HERNIOPLASTY-R	1
26	D	M	24	48	158	II	HERNIOPLASTY-L	1
27	D	M	29	50	160	II	EPIDIDYMALCYST	6
28	D	F	38	57	166	I	APPENDICECTOMY	1
29	C	F	42	60	156	I	INCISIONAL HERNIA	7
30	C	m	18	50	155	I	APPENDICITIS	2
31	C	m	51	56	158	II	APPENDICECTOMY	2
S. No.	**group**	**sex**	**age**	**wt**	**ht**	**ASA**	**Type of Sx**	**Sx type**
32	D	f	43	62	164	II	APPENDICULAR PERFORATION- LAP	2
33	C	M	27	50	158	I	APPENDICECTOMY	2
34	C	F	18	45	150	I	APPENDICECTOMY	2
35	C	M	26	54	172	I	APPENDICECTOMY	2
36	D	M	18	47	163	I	HERNIORAPHY	1
37	D	M	24	48	160	I	RT HERNIA REPAIR	1
38	D	M	40	55	165	I	HERNIORAPHY	1
39	C	M	45	65	160	I	OPEN URETHROTOMY	8
40	C	M	18	52	161	II	HERNIORAPHY	1
41	B	M	35	44	158	I	LEFT URS/DJ STENTING	8

42	B	M	57	60	180	I	OPEN URETHROTOMY	8
43	D	M	65	50	162	I	B/L HERNIOPLASTY	1
44	B	m	50	56	170	I	HERNIPLASTY-R	1
46	B	m	28	45	164	I	HERNIOPLASTY-R	1
47	B	m	50	60	172	II	HERNIOPLASTY-L	1
48	B	f	36	58	156	II	OVARIAN CYST	5
49	B	m	42	45	164	I	HERNIOPLASTY	1
50	B	f	36	56	161	II	INCISION HERNIA	7
51	B	f	46	50	148	I	INCISION HERNIA	1
52	B	m	37	70	160	II	HERNIPLASTY-R	1
53	B	m	20	40	158	II	HERNIOPLASTY-R	1
54	B	m	29	45	164	I	HERNIOPLASTY-L	1
55	B	m	35	68	161	I	HERNIPLASTY-R	1
56	B	m	25	50	163	I	HERNIOPLASTY-R	1
57	B	m	22	58	156	II	HERNIOPLASTY-L	1
58	B	m	50	70	154	I	HERNIPLASTY-R	1
59	B	m	38	49	156	II	HERNIOPLASTY-R	1
60	B	m	45	69	166	I	HERNIOPLASTY-L	1
61	B	m	38	54	165	I	HERNIPLASTY-R	1
62	B	m	22	49	162	I	HERNIOPLASTY-R	1
63	B	m	40	64	164	I	HERNIOPLASTY-L	1
64	B	f	36	50	168	II	vaginal hysterectomy	5
S. No.	**group**	**sex**	**age**	**wt**	**ht**	**ASA**	**Type of Sx**	**Sx type**
65	C	M	36	60	164	I	HERNIPLASTY-R	1
66	C	M	50	62	160	II	HERNIOPLASTY-R	1
67	C	M	46	54	156	II	HERNIOPLASTY-L	1
68	C	F	50	50	145	I	APPENDICECTOMY	2
69	C	M	36	56	158	II	APPENDICECTOMY	2
70	C	M	40	68	156	II	APR	3
71	C	F	36	44	163	I	APPENDICECTOMY	2
72	C	M	45	53	165	I	HERNIORAPHY	1
73	C	M	45	62	142	I	HERNIPLASTY-R	1
74	C	M	40	55	166	I	HERNIOPLASTY-R	1
75	C	M	26	49	150	I	HERNIOPLASTY-L	1
76	C	M	45	70	152	II	APPENDICECTOMY	2
77	C	M	36	45	157	II	APPENDICECTOMY	2
79	C	M	46	57	174	II	APPENDICECTOMY	2
80	C	M	26	54	154	I	HERNIPLASTY-R	1
81	C	M	21	45	158	II	HERNIOPLASTY-R	1
82	C	M	24	50	169	II	HERNIOPLASTY-L	1
83	C	M	38	64	149	I	VARICOSE	4
84	C	M	39	44	154	I	INCISIONAL HERNIA	7
85	C	M	45	60	142	I	INCISIONAL HERNIA	7
86	B	m	39	60	160	I	HERNIPLASTY-R	1

87	B	m	35	55	162	I	HERNIOPLASTY-R	1
88	B	M	41	60	155	I	HERNIOPLASTY-L	1
89	B	m	44	52	160	I	ORCHIDOPEXY	6
90	B	F	54	50	150	I	APPENNDICECTOMY	1
91	B	M	32	60	165	I	DJ STENTING	8
92	B	F	56	55	160	II	APPENDICECTOMY	4
93	B	f	27	65	170	I	VARICOSE VEIN	4
94	B	M	53	65	160	I	HERNIOPLASTY	1
95	B	M	28	55	155	I	HAEMORRHOIDECTOMY	9
96	B	F	46	50	150	I	VARICOSE	4

BsLin PR	PR 2	PR 5	PR 10	PR 15	PR 20	PR 25	PR 30	PR 35	PR 40	PR 45	PR 50	PR 55	PR 60	PR 70	PR 80	PR 90	PR 100	PR 110	PR 120	PR 130	PR 1
106	104	102	102	100	98	94	90	94	88	85	80	82	84	82	82	80	82	80	84	80	
84	80	82	80	84	68	68	68	70	74	70	70	74	72	70	70	72	70	73	75	73	
86	80	75	75	70	69	68	68	68	67	64	62	60	62	62	62	62	62	62	62	64	
88	86	86	87	86	85	86	86	86	86	86	87	84	84	84	82	80	80	80	80	80	
74	88	86	88	85	84	86	88	88	94	94	96	99	96	96	96	96	100	97	98	100	
75	67	71	86	87	83	82	80	88	86	90	87	88	87	85	95	95	94	92	90	90	
96	98	102	108	110	100	96	100	96	100	101	96	94	92	80	94	90	101	100	110	113	1
70	64	65	60	66	64	68	70	65	68	66	64	66	65	66	64	62	64	62	60	64	
52	50	48	48	58	60	60	60	56	56	56	52	52	52	52	52	52	48	46	49	52	
86	82	80	76	72	76	76	76	76	72	72	72	68	72	84	88	88	88	72	73	73	
96	94	92	92	90	92	88	88	100	104	100	92	92	84	84	80	84	84	84	84	80	
96	100	102	104	102	102	104	104	104	94	104	104	102	90	92	88	90	92	88	88	86	
90	89	88	86	80	80	78	80	82	80	80	80	82	80	78	74	74	75	74	76	74	
96	110	104	106	106	114	105	102	102	100	100	100	100	100	102	104	102	100	100	100	100	1
100	92	90	92	90	96	100	96	92	92	90	92	86	84	84	80	84	80	82	80	85	
74	76	76	98	84	80	78	80	76	76	78	78	78	78	76	76	74	74	74	76	76	
90	92	94	94	96	98	100	103	96	99	94	93	90	89	90	92	96	94	95	95	98	
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62	60	64	61	59	58	56	52	54	56	56	58	58	56	58	59	58	56	54	54	56	
78	76	76	74	78	76	76	76	76	74	75	76	75	76	74	75	72	76	75	76	74	
77	78	80	81	90	80	90	82	75	77	74	73	70	80	80	78	75	75	73	72	72	
76	84	88	88	78	74	78	78	70	74	74	78	80	86	86	92	78	76	78	78	80	
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94	92	86	84	76	70	72	72	78	78	80	84	82	84	86	86	86	84	84	84	82	
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90	90	84	80	76	70	68	66	68	70	68	70	70	70	70	70	72	68	70	68	68	
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75	75	72	72	88	85	86	85	84	79	83	86	84	71	77	78	85	88	84	85	86	
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76	84	88	88	78	74	78	78	70	74	74	78	80	86	86	92	78	76	78	78	80	
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68	68	68	64	58	60	64	64	72	70	68	68	64	60	62	66	64	66	64	66	65	
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97	100	100	98	96	96	97	78	82	80	82	80	76	73	73	92	88	94	100	100	98	
72	74	72	76	74	72	68	74	66	60	62	60	58	60	64	68	80	84	88	90	88	
94	90	92	92	94	92	96	96	92	90	90	92	90	93	88	88	86	84	84	82	85	
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74	74	74	72	72	76	72	76	78	76	72	70	68	64	60	60	62	72	78	80	76	
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SBPPREOP	SBP 2	SBP 5	SBP 10	SBP 15	SBP 20	SBP 25	SBP 30	Sbp 35	Sbp 40	SBP 45	SBP 50	SBP 55	SBP 60	SBP 70	SBP 80	SBP 90	SBP 100	SBP 110	SBP 120	SBP 130	SBP 140	SBP 150	SBP 160	SBP 175	SBP 190	SBP 205	SBP 220	S 2
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